Fasting Period	AUC (ng/ml.hr)	C_{max} (ng/ml)	T_{max} (hr)
Fed	7,826	1,574	2.4

Example 38 ***Bioadhesive Levodopa-Carbidopa 200 mg/50 mg Quadrilayer Tablets, Lot # 603-242***

Bioadhesive levodopa-carbidopa quadrilayer tablets were produced with wet granulation and compression in accordance with the method described in Example 9. Tablets comprised an active controlled release (CR) layer laminated between two passive bioadhesive layers, and an immediate release (IR) layer overlying one of the bioadhesive layers. The weight and composition of the IR, CR and bioadhesive layers are given in Table 16.

Table 16. Weight and Composition of Immediate Release, Controlled Release, and Bioadhesive Layers of Levodopa-Carbidopa 200 mg/50 mg Quadrilayer Tablet, Lot # 603-242

Immediate Release Layer		
Ingredients	**Weight %**	**Weight (mg)**
Levodopa, USP	33.3	40.0
Carbidopa monohydrate, USP	9.0	10.8
LUDIPRESS®	49.3	59.2
citric acid, anhydrous, USP	8.0	9.6
Magnesium Stearate, NF	0.3	0.3
Butylated hydroxytoluene, NF	0.1	0.1
Total	100.0	120.0

Controlled Release Layer		
Ingredients	**Weight %**	**Weight (mg)**
Levodopa, USP	43.5	159.6
Carbidopa monohydrate, USP	11.8	43.3
Succinic Acid, FCC	17.7	65.0
Hypromellose 2910, 5 cps, USP	14.3	52.5
Hypromellose 2208, 100 cps, USP	9.6	35.2
Corn Starch, NF	2.6	9.5
Magnesium Stearate, NF	0.4	1.5
Butylated hydroxytoluene, NF	0.1	0.4
Total	100.0	367.0

Bioadhesive Layer		
Ingredients	**Weight %**	**Weight (mg)**
SPHEROMER™ III	62.2	155.6
SPHEROMER™ I [p (FASA)]	21.6	54.0
Hydroxypropyl cellulose (KLUCEL® EF Pharm),	13.0	32.4
citric acid, anhydrous, USP	3.0	7.5
Magnesium Stearate, NF	0.2	0.5
Total	100.0	250.0

The ingredients of the IR layer excluding magnesium stearate were blended in a GlobePharma Maxiblend V-shell blender equipped with a 0.5-qt V-shell, for 10 min. Magnesium stearate was added to the mixed ingredients and the materials were blended for an additional 5 min.

The CR layer was prepared with the granulation method described in Example 4. The ingredients of the CR layer excluding Hypromellose 2910 and magnesium stearate were blended in a Hobart Mixer for 5 min. The dry blend was granulated by using a 5%

(w/v) solution of Hypromellose 2910 in methyl alcohol. The wet granulation was dried in a Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 200 lpm (liters per minute) and an inlet air temperature of 50 °C. The dried granulation was passed through a U.S. Std. mesh # 60 sieve. The screened granulation was mixed with magnesium stearate in the GlobePharma Maxiblend V-shell blender equipped with a 0.5-qt V-shell for 5 min.

SPHEROMER™ III was granulated along with hydroxypropyl cellulose (HPC) and citric acid by using a 3% (w/v) solution of HPC in methylene chloride in a Hobart Mixer in accordance with the method described in Example 5. The wet granulation was dried in the Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 290 lpm (liters per minute) and an inlet air temperature of 55 °C. The dried granulation was passed through a U.S. Std. mesh # 40 sieve.

SPHEROMER™ I was granulated along with hydroxypropyl cellulose (HPC) by using a 2% (w/v) solution of HPC in dehydrated alcohol in a Hobart Mixer in accordance with the method described in Example 5. The wet granulation was dried in the Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 200 lpm (liters per minute) and an inlet air temperature of 60 °C. The dried granulation was passed through a U.S. Std. mesh # 40 sieve.

The screened SPHEROMER™ III and SPHEROMER™ I granulations were blended in a GlobePharma Maxiblend V-shell blended equipped with a 2-qt V-shell, for 10 min. Magnesium stearate was added to the blend and the materials were mixed for an additional 5 min. The final blend was passed through a U.S. Std. mesh # 40 sieve.

A 0.3286" x 0.8937" standard capsule-shaped die and punch set was installed on GlobePharma Manual Tablet Compaction Machine MTCM-I. The quadrilayer tablet was prepared by pre-compression of the four layers at 500 psi (pound per square inch) for 2 seconds and final compression at 4000 psi for 2 s.

Example 39 ***In vitro Dissolution and In vivo Pharmacokinetic Performance of Bioadhesive Levodopa-Carbidopa 200 mg/50 mg Quadrilayer Tablets, Lot # 603-242***

The *in vitro* dissolution profile of bioadhesive levodopa-carbidopa quadrilayer tablets, containing 50 mg carbidopa and 200 mg levodopa was obtained under simulated gastric conditions. The dissolution tests were performed in 900 mL of 0.1 N HCl – pH 1.2

solution in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by HPLC. The dissolu-tion profiles of levodopa and carbidopa obtained from HPLC analysis are shown in Figure 60.

The *in vivo* performance of bioadhesive levodopa-carbidopa quadrilayer tablets was evaluated in beagle dogs. The tablets were administered to separate cohorts of six beagle dogs in the fed and fasted states. Plasma levels of levodopa and carbidopa were measured using LC/MS/MS analysis. Figures 61 and 62 show the plasma concentration profiles of levodopa and carbidopa in the fed and fasted states, respectively. The pharmacokinetic data including the area under the plasma levodopa vs. time curve (AUC), maximum concentration (C_{max}) and time required to achieve C_{max} (T_{max}) are provided in Table 17.

Table 17. Pharmacokinetic Data for Bioadhesive Levodopa-Carbidopa Quadrilayer Tablets, Lot # 603-242, in Fed and Fasted Beagle Dogs; the area under the plasma levodopa vs. time curve (AUC), maximum concentration (C_{max}), and time required to achieve C_{max} (T_{max})

Fasting Period	AUC (ng/ml.hr)	C_{max} (ng/ml)	T_{max} (hr)
Fed	16,558	1,798	10.3
Fasted	6,375	3,277	0.5

Example 40 ***Bioadhesive Levodopa-Carbidopa 200 mg/50 mg Quadrilayer Tablets, Lot # 603-243***

Bioadhesive levodopa-carbidopa quadrilayer tablets were produced with wet granulation and compression in accordance with the method described in Example 9. Tablets comprised an active controlled release (CR) layer laminated between two passive bioadhesive layers, and an immediate release (IR) layer overlying one of the bioadhesive layers. The weight and composition of the IR, CR and bioadhesive layers are given in Table 18.

Table 18. Weight and Composition of Immediate Release, Controlled Release, and Bioadhesive Layers of Levodopa-Carbidopa 200 mg/50 mg Quadrilayer Tablet, Lot # 603-243

Immediate Release Layer		
Ingredients	**Weight %**	**Weight (mg)**
Levodopa, USP	33.3	40.0
Carbidopa monohydrate, USP	9.0	10.8
LUDIPRESS®	49.3	59.2
citric acid, anhydrous, USP	8.0	9.6
Magnesium Stearate, NF	0.3	0.3
Butylated hydroxytoluene, NF	0.1	0.1
Total	100.0	120.0
Controlled Release Layer		
Ingredients	**Weight %**	**Weight (mg)**
Levodopa, USP	43.5	160.0
Carbidopa monohydrate, USP	11.7	42.9
Hypromellose 2208, 100 cps, USP	19.1	70.1
Succinic Acid, FCC	17.7	65.0
Hypromellose 2910, 5 cps, USP	4.8	17.6
Corn Starch, NF	1.7	6.2
Hypromellose 2208, 4000 cps, USP	1.0	3.7
Magnesium Stearate, NF	0.4	1.5
Butylated hydroxytoluene, NF	0.1	0.4
Total	100.0	367.0
Bioadhesive Layer		
Ingredients	**Weight %**	**Weight (mg)**
SPHEROMER™ III	62.2	155.6
SPHEROMER™ I [p (FASA)]	21.6	54.0
Hydroxypropyl cellulose (KLUCEL® EF Pharm),	13.0	32.4
citric acid, anhydrous, USP	3.0	7.5
Magnesium Stearate, NF	0.2	0.5
Total	100.0	250.0

The ingredients of the IR layer excluding magnesium stearate were blended in a GlobePharma Maxiblend V-shell blender equipped with a 0.5-qt V-shell, for 10 min. Magnesium stearate was added to the mixed ingredients and the materials were blended for an additional 5 min.

The CR layer was prepared with the granulation method described in Example 4. The ingredients of the CR layer excluding Hypromellose 2910 and magnesium stearate

were blended in a Hobart Mixer for 5 min. The dry blend was granulated by using a 5% (w/v) solution of Hypromellose 2910 in methyl alcohol. The wet granulation was dried in a Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 200 lpm (liters per minute) and an inlet air temperature of 50 °C. The dried granulation was passed through a U.S. Std. mesh # 60 sieve. The screened granulation was mixed with magnesium stearate in the GlobePharma Maxiblend V-shell blender equipped with a 0.5-qt V-shell for 5 min.

SPHEROMER™ III was granulated along with hydroxypropyl cellulose (HPC) and citric acid by using a 3% (w/v) solution of HPC in methylene chloride in a Hobart Mixer in accordance with the method described in Example 5. The wet granulation was dried in the Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 290 lpm (liters per minute) and an inlet air temperature of 55 °C. The dried granulation was passed through a U.S. Std. mesh # 40 sieve.

SPHEROMER™ I was granulated along with hydroxypropyl cellulose (HPC) by using a 2% (w/v) solution of HPC in dehydrated alcohol in a Hobart Mixer in accordance with the method described in Example 5. The wet granulation was dried in the Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 200 lpm (liters per minute) and an inlet air temperature of 60 °C. The dried granulation was passed through a U.S. Std. mesh # 40 sieve.

The screened SPHEROMER™ III and SPHEROMER™ I granulations were blended in a GlobePharma Maxiblend V-shell blended equipped with a 2-qt V-shell, for 10 min. Magnesium stearate was added to the blend and the materials were mixed for an additional 5 min. The final blend was passed through a U.S. Std. mesh # 40 sieve.

A 0.3286" x 0.8937" standard capsule-shaped die and punch set was installed on GlobePharma Manual Tablet Compaction Machine MTCM-I. The quadrilayer tablet was prepared by pre-compression of the four layers at 500 psi (pound per square inch) for 2 seconds and final compression at 4000 psi for 2 s.

Example 41 *In vitro* Dissolution and *In vivo* Pharmacokinetic Performance of Bioadhesive Levodopa-Carbidopa 200 mg/50 mg Quadrilayer Tablets, Lot # 603-243

The *in vitro* dissolution profile of bioadhesive levodopa-carbidopa quadrilayer tablets, containing 50 mg carbidopa and 200 mg levodopa was obtained under simulated

gastric conditions. The dissolution tests were performed in 900 mL of 0.1 N HCl – pH 1.2 solution in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by HPLC. The dissolu-tion profiles of levodopa and carbidopa obtained from HPLC analysis are shown in Figure 63.

The *in vivo* performance of bioadhesive levodopa-carbidopa quadrilayer tablets was evaluated in beagle dogs. The tablets were administered to separate cohorts of six beagle dogs in the fed and fasted states. Plasma levels of levodopa and carbidopa were measured using LC/MS/MS analysis. Figures 64 and 65 show the plasma concentration profiles of levodopa and carbidopa in the fed and fasted states, respectively. The pharmacokinetic data including the area under the plasma levodopa vs. time curve (AUC), maximum concentration (C_{max}) and time required to achieve C_{max} (T_{max}) are provided in Table 19.

Table 19. Pharmacokinetic Data for Bioadhesive Levodopa-Carbidopa Quadrilayer Tablets, Lot # 603-243, in Fed and Fasted Beagle Dogs; the area under the plasma levodopa vs. time curve (AUC), maximum concentration (C_{max}), and time required to achieve C_{max} (T_{max})

Fasting Period	AUC (ng/ml.hr)	C_{max} (ng/ml)	T_{max} (hr)
Fed	15,927	2,326	4.5
Fasted	7,175	3,073	0.9

Example 42 ***Manufacturing of Levodopa-Carbidopa (4:1) Core Pellets with Granulation-Extrusion-Spheronization, Lot # 606-027***

Levodopa-carbidopa core pellets (lot # 606-027) were prepared with granulation-extrusion-spheronization in accordance with the method described in Example 13. The dry weight and composition of pellets are given in Table 20. Micronized levodopa and carbidopa were blended with inactive excipients in a planetary mixer for 15 min. The levodopa-carbidopa-excipients blend was then granulated by spraying a 1.9% (w/v) aqueous solution of polyethylene oxide while mixing at low shear. The granulation was blended for an additional 5 min and then extruded through a 0.8 mm screen of a Caleva Extruder, model 25, operating at 10 rpm. The extrudate was spheronized in a Caleva Spheronizer, model 250, operating at 1250 rpm for 5 min. The spheronized pellets were dried in a Vector

MFL.01 Micro Batch Fluid Bed System at 50 °C for 90 minutes. The dried pellets were screened using # 16 and 35 mesh screens and particles with diameters ranging from 0.5 mm to 1.2 mm were selected for future experimentation.

Table 20. Dry Weight and Composition of Levodopa-Carbidopa Pellets, Lot # 606-027

Components	**Weight %**	**Weight (g)**
Levodopa, Micronized	33.71	202.28
Carbidopa, Monohydrate, USP	9.20	55.22
Fumaric Acid, NF	33.71	202.28
Microcrystalline Cellulose (EMCOCEL® 90 M), NF	15.31	91.83
Croscarmellose Sodium (AC-DI-SOL®), NF	4.80	28.81
Poloxamer 188 (LUTROL® F68), NF	2.70	16.21
Polyethylene Oxide (POLYOX™ WSR N10), NF	0.50	3.00
Butylated Hydroxytoluene, NF	0.06	0.38
Total	**100.00**	**600.00**

Example 43 ***Manufacturing and in vitro Dissolution of Levodopa-Carbidopa Bioadhesive Extended Release Pellets, Lot# 606-034***

Two hundred fifty grams of levodopa-carbidopa core pellets of lot # 606-027 retained on mesh # 35 (from Example 42) were subsequently coated in a Vector MFL.01 Micro Batch Fluid Bed System with a release rate-controlling composition containing EUDRAGIT® RS 100, EUDRAGIT® RL 100, ACRYL-EZE® and triethyl citrate (65:15:5:15) dissolved in methanol to achieve a weight gain of 4.4% (w/w). These pellets were subsequently film-coated with a bioadhesive polymeric composition comprising SPHEROMER™ III, succinic acid and citric acid (45:50:5) dissolved in methanol to achieve a weight gain of 6.9% (w/w). Finally they were top-coated with a hypromellose and OPADRY® Clear coating mixture (45:55) dissolved in a methanol and water solution (90:10 v/v) to achieve a weight gain of 2.4% (w/w). The top coating was added to keep pellets monodispersed upon release in the stomach.

Various film coatings were performed in the Vector MFL.01 Micro Batch Fluid Bed

System, equipped with a Wurster insert, operating at an inlet air flow rate of 100-300 lpm (liter per minute) and an inlet air temperature of 35 °C ± 5 °C. The pellets were pre-warmed at 35 °C for 2-5 min and after film-coating were post-dried at 30 °C for 15-30 min. The weight and composition of coated pellets (lot # 606-034) are given in Table 21. Figure 66 shows the *in vitro* dissolution profiles of levodopa and carbidopa obtained from HPLC analysis in phosphate buffered saline, pH 4.5.

Table 21. Weight and Composition of Levodopa-Carbidopa Bioadhesive Extended Release Pellets, Lot# 606-034

Components	Weight %	Weight (g)
Levodopa-Carbidopa Core Pellets (Lot # 606-027)	76.71	250.0
Succinic Acid, FCC	5.37	17.5
EUDRAGIT® RS 100, NF	5.00	16.3
SPHEROMER™ III	4.85	15.8
OPADRY® Clear	2.64	8.6
Hypromellose 2910, 5 cps (METHOCEL™ E5 Premium LV), USP	2.15	7.0
EUDRAGIT® RL 100, NF	1.17	3.8
Triethyl Citrate, NF	1.17	3.8
Anhydrous Citric Acid, USP	0.55	1.8
ACRYL-EZE® White (93O18509)	0.40	1.3
Total	**100.00**	**325.9**

Example 44 ***Manufacturing of Levodopa-Carbidopa Immediate Release Layer Blend, Lot # 606-052***

To manufacture a rapidly disintegrating matrix tablet of levodopa and carbidopa, a dry blend of these actives with inactive ingredients was prepared using a V-shell blender. The weight and composition of the blend are given in Table 22. All ingredients excluding magnesium stearate were blended in a GlobePharma Maxiblend V-shell blender equipped with a 2-qt V-shell, for 10 min. Magnesium stearate was added to the mixed ingredients and the materials were blended for an additional 5 min.

Table 22. Weight and Composition of Levodopa-Carbidopa Immediate Release Layer Blend, Lot# 606-052

Components	Weight %	Weight (g)
Levodopa, Micronized	4.80	24.00
Carbidopa, Monohydrate, USP	1.30	6.50
LUDIPRESS®	50.80	254.00
Microcrystalline Cellulose (AVICEL® PH-105), NF	26.00	130.00
Croscarmellose Sodium (AC-DI-SOL®), NF	15.00	75.00
Anhydrous Citric Acid, USP	1.10	5.50
Poloxamer 188 (LUTROL® F68), NF	0.59	2.95
Magnesium Stearate, NF	0.40	2.00
Butylated Hydroxytoluene, NF	0.01	0.05
Total	**100.00**	**500.00**

Example 45 ***Manufacturing and in vitro Dissolution of Levodopa-Carbidopa 200 mg/50 mg Rapidly Disintegrating Pelletized Extended Release Tablets, Lot # 606-058***

This formulation approach is a monolithic tablet system comprising a rapidly disintegrating levodopa-carbidopa matrix component and levodopa-carbidopa bioadhesive extended release multiparticulate pellets. The tablet disintegrates rapidly in the stomach releasing an initial dose of levodopa-carbidopa and the multiparticulate pellets into the gastric environment. This allows an initial dose of levodopa to be immediately absorbed. The multipar-ticulate pellets adhere to the gastric mucosal lining and release levodopa in a regulated manner.

Levodopa-carbidopa rapidly disintegrating pelletized tablets were prepared using direct compression. The manufacturing processes comprised:

(1) Weighing levodopa-carbidopa bioadhesive extended release pellets (lot # 606-034) prepared in accordance with Example 43.

(2) Weighing levodopa-carbidopa rapidly disintegrating layer blend (lot.# 606-052) prepared in accordance with Example 44.

(3) Mixing the weighed ingredients from steps 1 and 2 in a small container.

The tablets were produced using a single-station manual tablet press, GlobePharma Manual Tablet Compaction Machine MTCM-I, equipped with a 0.3287" x 0.8937" capsule-shaped die and punch set. The compression process comprised:

(4) Adding the mix from step 3 into the die cavity.

(5) Pre-compressing the mix at a pressure ranging from 200 psi (pounds per square inch) and a compression time of 5 seconds.

(6) Compressing the mix together at a pressure ranging from 1900 psi and a compression time of 5 seconds.

Figure 67 shows the *in* vitro dissolution profile of the levodopa-carbidopa rapidly disin-tegrating pelletized tablets obtained from HPLC analysis in phosphate buffered saline, pH 4.5.

Example 46 ***Manufacturing and in vitro Dissolution Testing of Levodopa-Carbidopa Bioadhesive Extended Release Pellets, Lot# 606-068***

Eighty grams of levodopa-carbidopa core pellets of lot # 606-027 retained on mesh # 35 (from Example 42) were subsequently coated in a Vector MFL.01 Micro Batch Fluid Bed System with a release rate-controlling composition containing EUDRAGIT® RS 100, EUDRAGIT® RL 100, ACRYL-EZE® and triethyl citrate to achieve a weight gain of 4.3% (w/w). These pellets were subsequently film-coated with a bioadhesive polymeric composition comprising SPHEROMER™ III, succinic Acid and citric acid (40:50:5) to achieve a weight gain of 4.2% (w/w). Finally they were top-coated with a SPHEROMER™ I and triethyl citrate (80:20) coating mixture to achieve a weight gain of 1% (w/w). The top coating was added to keep pellets monodispersed upon release in the stomach.

Various film coatings were performed in a fluidized bed coater, Vector MFL.01 Micro Batch Fluid Bed System, equipped with a Wurster insert, operating at an inlet air flow rate of 100±50 lpm (liter per minute) and an inlet air temperature of 35°C±5°C. The pellets were pre-warmed at 35°C for 5 min and after film-coating were post-dried at 30°C for 10 min. The weight and composition of coated pellets (lot # 606-068) are given in Table 23. Figure 68 shows the dissolution profiles of levodopa and carbidopa obtained from HPLC analysis in phosphate buffered saline, pH 4.5.

Table 23. Weight and Composition of Levodopa-Carbidopa Bioadhesive Extended Release Pellets, Lot# 606-068

Components	Weight (%)	Weight (g)
Levodopa-Carbidopa Core Pellets	91.11	80
EUDRAGIT® RS 100, NF	1.66	1.46
EUDRAGIT® RL 100, NF	1.66	1.46
Triethyl Citrate, NF	0.58	0.51
ACRYL-EZE® White (93O18509)	0.19	0.17
Succinic Acid, FCC	2.20	1.93
SPHEROMER™ III	1.59	1.4
Anhydrous Citric Acid, USP	0.20	0.18
SPHEROMER™ I	0.80	0.7
Total	100	87.81

Example 47 ***Manufacturing of Levodopa-Carbidopa Immediate Release Granules, Lot # 606-050***

Levodopa-carbidopa immediate-release (IR) granules were prepared by mixing the ingredients of the IR granules (Table 24) excluding hypromellose were blended in a low shear mixer followed by granulation using methanolic solution of hypromellose. The granules were dried using a fluidized bed dryer, Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 100-115 lpm (liter per minute) and an inlet air temperature of 50 °C for 2 hours. The granulation was then passed through a U.S. Std mesh #35 sieve.

Table 24. Weight and Composition of Levodopa-Carbidopa Immediate Release Granules, Lot# 606-050

Components	Weight (%)	Weight (g)
Levodopa, Micronized	32.30	38.96

Carbidopa, Monohydrate, USP	8.73	10.53
AVICEL® PH-105 (Microcrystalline Cellulose)	34.05	41.07
Croscarmellose Sodium (AC-DI-SOL®), NF	9.70	11.7
Poloxamer 188 (LUTROL® F68), NF	4.37	5.27
Butylated Hydroxytoluene, NF	0.10	0.12
Anhydrous Citric Acid, USP	7.76	9.36
Hypromellose 2910, 5 cps (METHOCEL™ E5 Premium LV), USP	2.98	3.6
Total	100.00	120.61

Example 48 ***Manufacturing of Bioadhesive Blend, Lot # 603-228***

Bioadhesive blend was prepared using SPHEROMER™ III and SPHEROMER™ I granulation. The composition is listed in Table 25. SPHEROMER™ III was granulated along with hydroxypropyl cellulose (HPC) and citric acid by using a 3% (w/v) solution of HPC in methylene chloride in a Hobart Mixer in accordance with the method described in Example 5. The wet granulation was dried in a Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 290 lpm (liter per minute) and an inlet air temperature of 55 °C. The dried granulation was passed through a U.S. Std. mesh # 40 sieve.

SPHEROMER™ I was granulated along with hydroxypropyl cellulose (HPC) by using a 2% (w/v) solution of HPC in dehydrated alcohol in a Hobart Mixer in accordance with the method described in Example 5. The wet granulation was dried in the Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 200 lpm (liter per minute) and an inlet air temperature of 60 °C. The dried granulation was passed through a U.S. Std. mesh # 40 sieve.

The screened SPHEROMER™ III and SPHEROMER™ I granulations were blended in a GlobePharma Maxiblend V-shell blender equipped with a 2-qt V-shell, for 10 min. Magnesium stearate was added to the blend and the materials were mixed for an additional 5 min. The final blend was passed through a U.S. Std. mesh # 40 sieve.

Table 25. Weight and Composition of Bioadhesive Blend, Lot# 603-228

Ingredients	Weight	Weight (mg)
SPHEROMER™ III	62.2	155.6
SPHEROMER™ I [p (FASA)]	21.6	54.0
Hydroxypropyl cellulose (KLUCEL® EF Pharm), NF	13.0	32.4
Citric Acid, anhydrous, USP	3.0	7.5
Magnesium Stearate, NF	0.2	0.5
Total	100.0	250.0

Example 49 ***Manufacturing of Slowly Eroding Matrix Blend, Lot # 606-072***

Slowly eroding matrix blend was prepared using a V-shell blender. The ingredients of the matrix blend (Table 26) excluding magnesium stearate were blended in a GlobePharma Maxiblend V-shell blender equipped with a 2-qt V-shell, for 10 min. Magnesium stearate was added to the mixed ingredients and the materials were blended for an additional 5 min.

Table 26. Weight and Composition of Bioadhesive Blend, Lot# 603-228

Ingredients	Weight %	Weight (mg)
Ethylcellulose (ETHOCEL™ Std 10 FP Premium),	32.5	243.75
Compressable Sugar, NF	45.2	339.00
Succinic Acid, FCC	7.0	52.50
Talc, USP	15.0	112.50
Magnesium Stearate, NF	0.3	2.25
Total	100.0	750.00

Example 50 ***Manufacturing and in vitro Dissolution of Levodopa-Carbidopa 200 mg/50 mg Slowly Eroding Pelletized Extended-Release Tablets, Lot # 606-072***

This formulation approach is a multilayer tablet system is a multilayer tablet system consisting of an immediate release (IR) levodopa-carbidopa component, a bioadhesive or optionally a non-bioadhesive backing layer and levodopa-carbidopa bioadhesive extended release multiparticulate beads embedded in an inner slowly eroding matrix. The bioadhesive

layer adheres to the gastric mucosa and further reduces variability by increasing the gastric residence time. The IR layer disintegrates rapidly releasing an initial dose of levodopa-carbidopa in the stomach. This allows an initial dose of levodopa and carbidopa to be immediately absorbed. The inner matrix layer of the tablet erodes slowly and evenly for 3 to 4 hours and releases the multiparticulate beads slowly. The multiparticulate beads adhere to the gastric mucosal lining and release levodopa and carbidopa in a regulated manner.

Levodopa-carbidopa slowly eroding pelletized extended-release tablets were prepared using direct compression. The manufacturing processes comprised:

(1) Weighing levodopa-carbidopa bioadhesive extended-release pellets (lot # 606-068) prepared in accordance with Example 46.

(2) Weighing levodopa-carbidopa immediate-release granules (lot # 606-050) prepared in accordance with Example 47.

(3) Weighing bioadhesive blend (lot # 603-228) prepared in accordance with Example 48.

(4) Weighing slowly eroding matrix blend (lot # 606-072) prepared in accordance with Example 49.

(5) Mixing the weighed ingredients from step (1) and step (4) in a small container.

The tablets were produced using a single-station manual tablet press, GlobePharma Manual Tablet Compaction Machine MTCM-I, equipped with a 0.3287" x 0.8937" capsule-shaped die and punch set. The compression process comprised:

(6) Adding the material from step (3), followed by step (5), and finally step (2) into the die cavity.

(7) Compressing the mix together at a pressure of 2500 psi (pounds per square inch) and a compression time of 5 seconds.

Figure 69 shows the *in* vitro dissolution profile of the levodopa-carbidopa slowly eroding pelletized extended-release tablets (lot # 606-072) in phosphate buffered saline, pH 4.5.

The following examples relates to the multiparticulate formulation.

Example 51 ***Production of Levodopa, Carbidopa, and Levodopa-Carbidopa Pellets with Granulation-Extrusion-Spheronization and Fluid Bed Drying***

Levodopa, carbidopa, and levodopa-carbidopa pellets were produced with

granulation-extrusion-spheronization and fluid bed drying. The following steps (or minor variations thereof) may be followed to produce the pellets:

(1) Weighing levodopa or carbidopa, or both levodopa and carbidopa, optionally a bioadhesive polymer composition, and pharmaceutically acceptable excipients.

(2) Blending levodopa or carbidopa, or both levodopa and carbidopa, and optionally a bioadhesive polymer composition, with pharmaceutically acceptable excipients in a planetary type mixer, *e.g.*, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5-15 min, forming a dry mix.

(3) Granulating the dry mix from step (2) under low shear with a granulation fluid, forming a wet granulation. The granulation fluids were mainly selected from, *e.g.*, purified water, an aqueous solution of a mineral or organic acid, an aqueous solution of a polymeric composition, a pharmaceutically acceptable alcohol, a ketone or a chlorinated solvent, a hydro-alcoholic mixture, an alcoholic or hydro-alcoholic solution of a polymeric composition, a solution of a polymeric composition in a chlorinated solvent or in a ketone.

(4) Extruding the wet granulation from step (3) through the screen of a screen-type extruder, *e.g.*, Caleva Model 20 (or Model 25) Extruder, operating at 10-20 rpm, and forming breakable wet strands, the extrudate. The screen aperture was 0.8, 1, or 1.5 mm.

(5) Spheronizing the extrudate from step (4) in a spheronizer, *e.g.*, Caleva Model 250, equipped with a 2.5-mm spheronization plate, operating at 1000-2000 rpm for 5-10 min, and forming spheronized pellets.

(6) Drying the spheronized pellets from step (5) in a fluidized bed drier, *e.g.*, Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 100-300 lpm (liters per minute) and an inlet air temperature of 50 °C. Alternatively, pellets were dried either in an ACT (Applied Chemical Technology) fluidized bed drier or in a conventional Precision oven. The ACT fluidized bed drier was operated at an inlet air flow rate of 140-150 fpm (foot per minute) and an inlet air temperature of 104 °F. The oven was set at 50 °C.

(7) Screening and classifying the dried pellets from step (6) through a stack of stainless steel sieves, U.S. standard mesh sizes 8, 10, 12, 14, 16, 18, 20, 25, 30, 40, 45, and 60 using a mechanical sieve shaker, W.S. Tyler Sieve Shaker Ro-Tap Rx-29, operated for 5 min. Particle size and distribution of pellet formulations were analyzed,

and classified pellets ranging from 0.25 mm (mesh # 60) to 2 mm (mesh # 10) were selected for future film coating or other experimentation.

Example 52 ***Production of Levodopa, Carbidopa, and Levodopa-Carbidopa Pellets with Granulation-Extrusion-Spheronization and Oven Drying***

Levodopa, carbidopa, and levodopa-carbidopa pellets were produced with granulation-extrusion-spheronization and oven drying. The production processes included the steps 1 to 5 and 7 of Example 51 but the spheronized pellets were dried in a Precision gravity oven, operating at 50 °C, for 8-24 h.

Example 53 ***Film coating of Levodopa, Carbidopa, and Levodopa-Carbidopa Pellets with Bioadhesive Polymer, SPHEROMER™ I [poly(FASA)]***

Levodopa, carbidopa, and levodopa-carbidopa pellets were film-coated with a bioadhesive polymeric composition, SPHEROMER™ I [poly(FASA)]. Bioadhesive SPHEROMER™ I and optionally a functional polymer, or a non-functional polymer, and optionally pharmaceutically acceptable excipients, were dissolved in methylene chloride. The film coating was performed in a fluidized bed coater, Vector MFL.01 Micro Batch Fluid Bed System, equipped with a Wurster insert, operating at an inlet air flow rate of 100-300 lpm (liters per minute) and an inlet air temperature of 25 °C to 30 °C. The pellets were pre-warmed at 35 °C for 2-5 min and after film-coating were post-dried at 30 °C for 15-30 min.

Example 54 ***Film coating of Levodopa, Carbidopa, and Levodopa-Carbidopa Pellets with Bioadhesive Polymer, SPHEROMER™ III***

Levodopa, carbidopa, and levodopa-carbidopa pellets were film-coated with a bioadhesive polymeric composition, SPHEROMER™ III. Bioadhesive SPHEROMER™ III and optionally a functional polymer, or a non-functional polymer, and optionally pharmaceutically acceptable excipients, were dissolved in methanol. The film coating was performed in a fluidized bed coater, Vector MFL.01 Micro Batch Fluid Bed System, equipped with a Wurster insert, operating at an inlet air flow rate of 100-300 lpm (liter per minute) and an inlet air temperature of 35 °C±2 °C. The pellets were pre-warmed at 35 °C for 2-5 min and after film-coating were post-dried at 30 °C for 15-30 min.

Alternatively, pellets were coated in a Fluid Air Model 5 fluid bed processor,

equipped with a Wurster insert, operating at an inlet air flow rate of 70 cfm (cubic foot per minute) and an inlet air temperature of 35 °C. The pellets were pre-warmed at 40 °C for 5-7 min and after film-coating were post-dried at 35 °C for 30 min.

Example 55 ***Film coating of Levodopa, Carbidopa, and Levodopa-Carbidopa Pellets with Bioadhesive Polymeric Composition Comprising SPHEROMER™ I [poly(FASA)] and SPHEROMER™ III***

Levodopa, carbidopa, and levodopa-carbidopa pellets were film-coated with a bioadhesive polymeric composition of SPHEROMER™ I [poly(FASA)] and SPHEROMER™ III. Bioadhesive SPHEROMER™ I [poly(FASA)] and SPHEROMER™ III polymers, and optionally a functional polymer, or a non-functional polymer, and optionally pharmaceutically acceptable excipients, were dissolved in a binary mixture of methanol and methylene chloride. The film coating was performed in a fluidized bed coater, Vector MFL.01 Micro Batch Fluid Bed System, equipped with a Wurster insert, operating at an inlet air flow rate of 100-300 lpm (liter per minute) and an inlet air temperature of 25 °C to 35 °C. The pellets were pre-warmed at 35 °C for 2-5 min and after film-coating were post-dried at 30 °C for 15-30 min.

Example 56 ***Film coating of Levodopa, Carbidopa, and Levodopa-Carbidopa Pellets with Bioadhesive Polymer, SPHEROMER™ IV***

Levodopa, carbidopa, and levodopa-carbidopa pellets were film-coated with a bioadhesive polymeric composition, SPHEROMER™ IV. Bioadhesive SPHEROMER™ IV and optionally a functional polymer, or a non-functional polymer, were dissolved in methanol or a binary mixture of ethanol and water (3:1 v/v). The film coating was performed in a fluidized bed coater, Vector MFL.01 Micro Batch Fluid Bed System, equipped with a Wurster insert, operating at an inlet air flow rate of 100-300 lpm (liter per minute) and an inlet air temperature of 35 °C. The pellets were pre-warmed at 35 °C for 2-5 min and after film coating were post-dried at 30 °C for 15-30 min.

Example 57 ***Film coating of Levodopa, Carbidopa, and Levodopa-Carbidopa Pellets with a Functional or a Non-functional Polymer***

Levodopa, carbidopa, and levodopa-carbidopa pellets were film coated with a functional or a non-functional polymer. The polymer was dissolved in either of methanol,

ethanol, or isopropanol, or their binary mixture with acetone. The film coating was performed in a fluidized bed coater, Vector MFL.01 Micro Batch Fluid Bed System, equipped with a Wurster insert, operating at an inlet air flow rate of 100-300 lpm (liter per minute) and an inlet air temperature of 30 °C to 40 °C. The pellets were pre-warmed at 30 °C to 40 °C for 2-5 min and after film coating were post-dried at 30 °C to 40 °C for 15-30 min.

Example 58 ***Production of Carbidopa Granules with Low Shear Granulation and Fluid Bed Drying***

Carbidopa granules were produced with low shear granulation method comprising the following processes:

(1) Weighing carbidopa, optionally a bioadhesive polymer composition, and pharmaceutically acceptable excipients.

(2) Blending carbidopa, and optionally a bioadhesive polymer composition, with pharmaceutically acceptable excipients in a planetary type mixer, *e.g.*, Hobart Mixer, operating at the speed setting #1, for 5-15 min, forming a dry mix.

(3) Granulating the dry mix from step (2) under low shear with a granulation fluid, forming a wet granulation. The granulation fluid were mainly selected from purified water, an aqueous solution of a mineral or organic acid, an aqueous solution of a polymeric composition, an alcohol, a hydro-alcoholic mixture, or an alcoholic or hydro-alcoholic solution of a polymeric composition.

(4) Drying the granulation from step (3) in a fluidized bed drier, *e.g.*, Vector MFL.01 Micro Batch Fluid Bed System, operating at an inlet air flow rate of 100-300 lpm (liters per minute) and an inlet air temperature of 50 °C. Alternatively, the granulation from step (3) was dried in a Precision gravity oven, operating at 50 °C, for 8-24 h.

(5) Screening and classifying the dried granules from step (4) through a stack of stainless steel sieves, U.S. standard mesh sizes 20 and 60, using a mechanical sieve shaker, W.S. Tyler Sieve Shaker Ro-Tap Rx-29, operated for 5 min. Particle size and distribution of granular formulations were analyzed, and classified granules ranging from 0.25 mm (mesh # 60) to 0.85 mm (mesh # 20) were selected for future experimentation.

Example 59 ***Production of Carbidopa Granules with Low Shear Granulation and Oven***

Drying

Carbidopa granules were produced with low shear granulation and oven drying. The production processes included the steps 1 to 3 and 5 of Example 58 but the granulation was dried in a Precision gravity oven, operating at 50 °C, for 8-48 h.

Example 60 ***In vitro Dissolution of Multiparticulate Formulations of Levodopa, Carbidopa, and Levodopa-Carbidopa***

The *in vitro* dissolution profile of levodopa, carbidopa, and levodopa-carbidopa multiparticulate formulations were obtained under simulated gastric conditions. The dissolution tests were performed in 900 mL of either of 0.1 N HCl - pH 1.2, phosphate buffer saline (PBS) pH 4.5, or sodium acetate buffer pH 4.5 solutions, in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by either HPLC or UV spectrophotometry.

Example 61 ***In vitro Dissolution of SINEMET® 10-100 Tablets, containing 10 mg Carbidopa and 100 mg Levodopa, Lot # 00067***

The *in vitro* dissolution profile of SINEMET® 10-100 tablets, containing 10 mg carbidopa and 100 mg levodopa was obtained under simulated gastric conditions. The dissolution tests were performed in 900 mL of either of 0.1N HCl - pH 1.2, phosphate buffer saline (PBS) - pH 4.5, or sodium acetate buffer - pH 4.5 solutions, in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by UV spectrophotometry. The combined dissolution profile of levodopa-carbidopa obtained from UV spectrophotometry analysis is shown in Figure 70.

Example 62 ***In vitro Dissolution of SINEMET® CR 50-200 Tablets, containing 50 mg Carbidopa and 200 mg Levodopa, Lot # N4682***

The *in vitro* dissolution profile of SINEMET® CR 50-200 tablets, containing 50 mg carbidopa and 200 mg levodopa were obtained under simulated gastric conditions. The dissolution tests were performed in 900 mL of 0.1N HCl - pH 1.2 solution, in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by HPLC. The

dissolution profiles of levodopa and carbidopa obtained from HPLC analysis are shown in Figure 71.

Example 63 ***In vivo Pharmacokinetic Performance of SINEMET® 10-100 Tablets in Fed Beagle Dogs, Lot # 00067***

The *in vivo* performance of SINEMET® 10-100 tablets was evaluated in beagle dogs. SINEMET® tablets were administered to cohorts of six beagle dogs in the fed state and plasma levels of levodopa and carbidopa were measured using LC/MS/MS analysis. Figure 72 shows the plasma concentration profiles of levodopa and carbidopa. The pharmacokinetic data including the area under the plasma levodopa vs. time curve (AUC), maximum concentration (C_{max}) and time required to achieve C_{max} (T_{max}) are provided in Table 1A.

Table 1A. Pharmacokinetic Data for SINEMET® 10-100 Tablets, Lot # 00067, in Fed Beagle Dogs; the area under the plasma levodopa vs. time curve (AUC), maximum concentration (C_{max}), and time required to achieve C_{max} (T_{max})

Formulation	AUC (ng/ml.hr)	C_{max} (ng/ml)	T_{max} (hr)
SINEMET® 10-100 Tablets	5,956	3,400	0.66

Example 64 ***In vivo Pharmacokinetic Performance of SINEMET® CR 50-200 Tablets in Fed Beagle Dogs, Lot # N4682***

The *in vivo* performance of SINEMET® CR 50-200 tablets was evaluated in beagle dogs. SINEMET® CR tablets were administered to cohorts of six beagle dogs in the fed state and plasma levels of levodopa and carbidopa were measured using HPLC analysis. Figure 73 shows the plasma concentration profiles of levodopa and carbidopa. The pharmacokinetic data including the area under the plasma levodopa vs. time curve (AUC), maximum concentration (C_{max}) and time required to achieve C_{max} (T_{max}) are provided in Table 2A.

Table 2A. Pharmacokinetic Data for SINEMET® CR 50-200 Tablets, Lot # N4682, in Fed Beagle Dogs; the area under the plasma levodopa vs. time curve (AUC), maximum concentration (C_{max}), and time required to achieve C_{max} (T_{max})

Formulation	AUC (ng/ml.hr)	C_{max} (ng/ml)	T_{max} (hr)
SINEMET® CR 50-200 Tablets	3,903	1,663	2

Example 65 ***In vivo Pharmacokinetic Performance of SINEMET® CR 50-200 Tablets in Fasted Beagle Dogs, Lot # N4682***

The *in vivo* performance of SINEMET® CR 50-200 tablets was evaluated in beagle dogs. SINEMET® CR tablets were administered to cohorts of twelve beagle dogs in the fasted state and plasma levels of levodopa and carbidopa were measured using HPLC analysis. Figure 74 shows the plasma concentration profiles of levodopa and carbidopa. The pharmacokinetic data including the area under the plasma levodopa vs. time curve (AUC), maximum concentration (C_{max}) and time required to achieve C_{max} (T_{max}) are provided in Table 3A.

Table 3A. Pharmacokinetic Data for SINEMET® CR 50-200 Tablets, Lot # N4682, in Fasted Beagle Dogs; the area under the plasma levodopa vs. time curve (AUC), maximum concentration (C_{max}), and time required to achieve C_{max} (T_{max})

Formulation	AUC (ng/ml.hr)	C_{max} (ng/ml)	T_{max} (hr)
SINEMET® CR 50-200 Tablets	936	604	1

Example 66 ***Production of Levodopa Pellets with Granulation-Extrusion-Spheronization, Lot # 510-095***

Three identical sub-lots of levodopa pellets (sub-lots # 511-068, 511-069, and 511-070) were prepared in accordance with the method described in Example 51. The weight and composition of pellets of the sub-lot # 511-068 are given in Table 4A. Levodopa was blended with inactive excipients for 5 min. The levodopa-excipients blend was then

granulated by spraying purified water while mixing at low shear. The granulation was blended for an additional 5 min and then extruded through a 1.5 mm screen of a Caleva extruder, model 25, operating at 15 rpm. The extrudate was spheronized in a Caleva spheronizer, model 250, operating at 1000 rpm for 5 min. The spheronized pellets were dried in an ACT (Applied Chemical Technology) fluidized bed drier at 104 °F±4 °F for 75 min. The dried pellets were screened and particles with diameters ranging from 1 mm to 2 mm were selected for future experimentation. The screened pellets of the three sub-lots were blended in a GlobePharma Maxiblend Blender equipped with an 8-qt stainless steel V-shell.

Table 4A. Weight and Composition of Levodopa Pellets, Sub-lot # 511-068

Ingredients	**Weight %**	**Weight (g)**
Levodopa, USP	50.0	300
Microcrystalline cellulose (EMCOCEL® 90 M), NF	25.0	150
Mannitol (MANNOGEM™ Powdered), USP	14.0	84
Hydroxypropylcellulose (HPC-SSL), NF	5.0	30
Croscarmellose sodium (AC-DI-SOL®), NF	5.0	30
Citric acid, anhydrous, USP	1.0	6
Total	100.0	600

Example 67 ***Production of Levodopa-Carbidopa (4:1) Pellets with Granulation-Extrusion-Spheronization, Lot # 510-096***

Three identical sub-lots of levodopa-carbidopa pellets (sub-lots # 510-094, 511-043, and 511-055) were prepared in accordance with the method described in Example 51. The weight and composition of the sub-lot # 510-094 are given in Table 5A. Levodopa and carbidopa were blended with inactive excipients for 5 min. The levodopa-carbidopa-excipients blend was then granulated by spraying purified water while mixing at low shear. The granulation was blended for an additional 5 min and then extruded through a 1.5 mm screen of a Caleva extruder, model 25, operating at 15 rpm. The extrudate was spheronized in a Caleva spheronizer, model 250, operating at 1000 rpm for 5 min. The spheronized pellets were dried in an ACT (Applied Chemical Technology) fluidized bed drier at 104 °F ± 4 °F for 25 min. The dried pellets were screened and particles with diameters ranging

from 1 mm to 2 mm were selected for future experimentation. The screened pellets of the three sub-lots were blended in a GlobePharma Maxiblend Blender equipped with an 8-qt stainless steel V-shell.

Table 5A. Weight and Composition of Levodopa-Carbidopa Pellets, Sub-lot # 510-094

Ingredients	**Weight %**	**Weight (g)**
Levodopa, USP	50.0	300
Carbidopa monohydrate, USP	13.5	81
Microcrystalline cellulose (EMCOCEL® 90 M),	25.0	150
Hydroxypropylcellulose (HPC-SSL), NF	5.5	33
Lactose monohydrate (FASTFLO® 316), NF	5.0	30
Citric acid, anhydrous, USP	1.0	6
Total	100.0	600

Example 68 ***Production of Carbidopa Granules with Low Shear Granulation, Lot # 511-101***

Carbidopa granules were prepared in accordance with the method described in Example 59. The weight and composition of granules are given in Table 6A. Carbidopa was blended with inactive excipients for 5 min. The carbidopa-excipients blend was then granulated by spraying purified water while mixing at low shear. The granulation was blended for an additional 5 min and then dried in a Precision gravity oven at 50 °C for 41.5 hours. The dried granules were screened and particles smaller than 0.85 mm were selected for future experimentation.

Table 6A. Weight and Composition of Carbidopa Granules, Lot # 511-101

Ingredients	Weight %	Weight (g)
Carbidopa monohydrate, USP	52.0	104
Microcrystalline cellulose (EMCOCEL® 90 M),	23.5	47
Mannitol (MANNOGEM™ Powdered), USP	13.5	27
Hydroxypropylcellulose (HPC-SSL), NF	5.0	10
Croscarmellose sodium (AC-DI-SOL®), NF	5.0	10
Citric acid, anhydrous, USP	1.0	2
Total	100.0	200

Example 69 ***Film coating of Levodopa Pellets with Bioadhesive Polymer, SPHEROMER™ III, and Hydroxypropylcellulose (HPC-SSL), Lot # 511-092***

One thousand grams of levodopa pellets, lot # 510-095, were film-coated in a Fluid Air Model 5 fluid bed processor, equipped with a Wurster insert, in accordance with the method described in Example 54. The composition of coating solution is given in Table 7A. SPHEROMER™ III and Hydroxypropylcellulose (HPC-SSL) were dissolved in methanol and sprayed onto the fluidized pellets to obtain a 12% weight gain on pellets.

Table 7A. Composition of SPHEROMER™ III/Hydroxypropylcellulose (HPC-SSL) Coating Solution, Lot # 511-092

Ingredients	Weight %	Weight (g)
SPHEOROMER™ III	80.0	120
Hydroxypropylcellulose (HPC SSL), NF	20.0	30
Methyl alcohol, NF	*	(3,000 mL)
Total	100.0	150

* Methyl alcohol is removed during the coating/drying process.

Example 70 ***Film coating of Levodopa-Carbidopa Pellets with Bioadhesive Polymer, SPHEROMER™ III, Lot # 510-098***

One thousand grams of levodopa-carbidopa pellets, lot # 510-096, were film-coated in a Fluid Air Model 5 fluid bed processor, equipped with a Wurster insert, in accordance with the method described in Example 54. The composition of coating solution is given in

Table 8A. SPHEROMER™ III and Poloxamer 188 (Lutrol® F68) were dissolved in methanol and sprayed onto the fluidized pellets to obtain a 6% weight gain on pellets.

Table 8A. Composition of SPHEROMER™ III Coating Solution, Lot # 511-098

Ingredients	**Weight %**	**Weight (g)**
SPHEOROMER™ III	94.7	71
Poloxamer 188 (LUTROL® F68), NF	5.3	4
Methyl alcohol, NF	*	(1,500 mL)
Total	100.0	150

* Methyl alcohol is removed during the coating/drying process.

Example 71 ***Preparation of Levodopa-Carbidopa 200 mg/50 mg Multiparticulate Capsules, Lots # 510-099 & 510-100***

Levodopa pellets (lot # 510-095), SPHEROMER™ III-coated levodopa-carbidopa pellets (lot # 510-098), HPC-SSL/SPHEROMER™ III-coated levodopa pellets (lot # 511-092), and carbidopa granules (lot # 511-101) were encapsulated in 00-size hard gelatin capsules. Each capsule contained 200 mg levodopa and 50 mg carbidopa anhydrous. The composition of multiparticulates in each capsule formulation is given in Table 9A.

Table 9A. Composition (mg) of Multiparticulate Capsule Formulations, Lot # 510-099 & 510-100

Components	**Lot #**	**510-099**	**510-100**
Levodopa Pellets	510-095	80	80
SPHEROMER III-coated Levodopa-Carbidopa Pellets	510-098	340	255
HPC-SSL/SPHEROMER™ III-coated Levodopa	511-092	-	90
Carbidopa Granules	511-101	20	40
Total (mg per capsule)	-	440	

Example 72 ***In vitro Dissolution and In vivo Pharmacokinetic Performance of Levodopa-Carbidopa 200 mg/50 mg Multiparticulate Capsules, Lot # 510-***

099

The *in vitro* dissolution profile of levodopa-carbidopa capsules (Lot # 510-099), containing 50 mg carbidopa and 200 mg levodopa was obtained under simulated gastric conditions. The dissolution tests were performed in 900 mL of 0.1 N HCl – pH 1.2 solution in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by HPLC. The dissolu-tion profiles of levodopa and carbidopa obtained from HPLC analysis are shown in Figure 75.

The *in vivo* performance of levodopa-carbidopa capsules was evaluated in beagle dogs. The capsules were administered to separate cohorts of six beagle dogs in the fed and the fasted states. Plasma levels of levodopa and carbidopa were measured using LC/MS/MS analysis. Figures 76 and 77 show the plasma concentration profiles of levodopa and carbidopa in the fed and fasted states, respectively. The pharmacokinetic data including the area under the plasma levodopa vs. time curve (AUC), maximum concentration (C_{max}) and time required to achieve C_{max} (T_{max}) are provided in Table 10A.

It is apparent that, compared to the *in vivo* pharmacokinetic performance of SINEMET® CR 50-200 Tablets in similarly fed beagle dogs, the AUC of the subject formulation is more than 3 times that of the SINEMET® CR 50-200 Tablets, while the C_{max} is about the same. Furthermore, the T_{max} of the subject formulation is more than twice that of the SINEMET® CR 50-200 Tablets (e.g., 4.3 hrs compared to 2 hrs).

The results are even more pronounced in similarly fasted beagle dogs.

Table 10A. Pharmacokinetic Data for levodopa-carbidopa capsules, Lot # 510-099, in Fed and Fasted Beagle Dogs; the area under the plasma levodopa vs. time curve (AUC), maximum concentration (C_{max}), and time required to achieve C_{max} (T_{max})

Fasting Period	AUC (ng/ml.hr)	C_{max} (ng/ml)	T_{max} (hr)
Fed State	12,581	1,705	4.3
Fasted State	4,678	2,743	1

Example 73 ***In vitro Dissolution and In vivo Pharmacokinetic Performance of Levodopa-Carbidopa 200 mg/50 mg Multiparticulate Capsules, Lot # 510-***

100

The *in vitro* dissolution profile of levodopa-carbidopa capsules (Lot # 510-100), containing 50 mg carbidopa and 200 mg levodopa was obtained under simulated gastric conditions. The dissolution tests were performed in 900 mL of 0.1N HCl – pH 1.2 solution in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by HPLC. The dissolu-tion profiles of levodopa and carbidopa obtained from HPLC analysis are shown in Figure 78.

The *in vivo* performance of levodopa-carbidopa capsules was evaluated in beagle dogs. The capsules were administered to separate cohorts of six beagle dogs in the fed and the fasted states. Plasma levels of levodopa and carbidopa were measured using LC/MS/MS analysis. Figures 79 and 80 show the plasma concentration profiles of levodopa and carbidopa in the fed and fasted states, respectively. The pharmacokinetic data including the area under the plasma levodopa vs. time curve (AUC), maximum concentration (C_{max}) and time required to achieve C_{max} (T_{max}) are provided in Table 11A.

Under this formulation, it is apparent that, compared to the *in vivo* pharmacokinetic performance of SINEMET® CR 50-200 Tablets in similarly fed beagle dogs, the AUC of the subject formulation is more than 4 times that of the SINEMET® CR 50-200 Tablets, while the C_{max} is about 50% higher. Furthermore, the T_{max} of the subject formulation is about 2.5 times that of the SINEMET® CR 50-200 Tablets (e.g., 5 hrs compared to 2 hrs).

The results are even more pronounced in similarly fasted beagle dogs.

Table 11A. Pharmacokinetic Data for levodopa-carbidopa capsules, Lot # 510-100, in Fed and Fasted Beagle Dogs; the area under the plasma levodopa vs. time curve (AUC), maximum concentration (C_{max}), and time required to achieve C_{max} (T_{max})

Fasting Period	AUC (ng/ml.hr)	C_{max} (ng/ml)	T_{max} (hr)
Fed	16,811	2,518	5
Fasted	5,872	2,113	1.2

Example 74 ***Production and In vitro Dissolution of Levodopa-Carbidopa (4:1) Pellets, Sub-lots # 602-042 & 602-043***

Two identical sub-lots of levodopa-carbidopa pellets (sub-lots # 602-042 and 602-043) were prepared in accordance with the method described in Example 51. The weight and composition of pellets of the sub-lot # 602-042 are given in Table 12A. Levodopa and carbidopa were blended with inactive excipients for 15 min. The levodopa-carbidopa-excipients blend was then granulated by spraying a 1% (w/v) aqueous solution of polyethylene oxide (Polyox™ WSR N10) while mixing at low shear. The granulation was blended for an additional 5 min and then extruded through a 1.5 mm screen of a Caleva extruder, model 25, operating at 10 rpm. The extrudate was spheronized in a Caleva spheronizer, model 250, operating at 1000 rpm for 5 min. The spheronized pellets were dried in a Vector MFL.01 Micro Batch Fluid Bed System at 50 °C for 190 min. The dried pellets were screened and particles with diameters ranging from 1 mm to 2 mm were selected for future experimentation.

Table 12A. Weight and Composition of Levodopa-Carbidopa Pellets, Sub-lot # 602-042

Ingredients	**Weight %**	**Weight (g)**
Levodopa, USP	59.11	90.00
Carbidopa monohydrate, USP	15.95	24.29
Microcrystalline cellulose (EMCOCEL® 90 M), NF	14.78	22.50
L-Glutamic acid, FCC	9.75	14.85
Polyethylene oxide (POLYOX™ WSR N10), NF	0.31	0.47
Butylated hydroxytoluene (BHT), NF	0.10	0.15
Total	100.00	152.26

Aliquots of screened pellets, lot # 602-043, were encapsulated in 00-size hard gelatin capsules. The *in vitro* dissolution profile of levodopa-carbidopa capsules, containing 200 mg levodopa and 50 mg carbidopa anhydrous was obtained under simulated gastric conditions. The dissolution test was performed in 900 mL of 0.1 N HCl - pH 1.2 solution in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution medium were collected at predetermined intervals and analyzed by online UV spectrophotometry. The combined dissolution profile of levodopa-carbidopa obtained from UV analysis is shown in Figure 81.

Example 75 ***Production and In vitro Dissolution of SPHEROMER™ III/EUDRAGIT® RS 100-coated Levodopa-Carbidopa Pellets, Lot # 603-139***

Fifty grams of levodopa-carbidopa pellets, a blend of sub-lots # 602-042 and 602-043, were film-coated in a Vector MFL.01 Micro Batch Fluid Bed System, equipped with a Wurster insert, in accordance with the method described in Example 54. The screened pellets of the two sub-lots were blended in the fluid bed system by fluidization prior to film-coating. The composition of coating solution is given in Table 13A. SPHEROMER™ III, EUDRAGIT® RS 100, and anhydrous citric acid were dissolved in methanol and sprayed onto the fluidized pellets to obtain a 12% weight gain on pellets.

Table 13A. Composition of SPHEROMER™ III/EUDRAGIT® RS 100 Coating Solution, Lot # 603-139

Ingredients	**Weight %**	**Weight (g)**
Spheoromer™ III	85	5.1
EUDRAGIT® RS 100	10	0.6
Anhydrous citric acid, USP	5	0.3
Methyl alcohol, NF	*	(150 mL)
Total	100.0	6.0

* Methyl alcohol is removed during the coating/drying process.

Aliquots of coated pellets were encapsulated in 00-size hard gelatin capsules.

The *in vitro* dissolution profile of levodopa-carbidopa capsules, containing 200 mg levodopa and 50 mg carbidopa anhydrous was obtained under simulated gastric conditions. The dissolution test was performed in 900 mL of either of 0.1N HCl - pH 1.2 or phosphate buffer saline (PBS) – pH 4.5 solutions in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution medium were collected at predetermined intervals and analyzed by online UV spectrophotometry. The combined dissolution profiles of levodopa-carbidopa obtained from UV analysis are shown in Figure 82.

Example 76 ***Production and In vitro Dissolution of Immediate Release Levodopa-Carbidopa (4:1) Pellets, Lot # 603-069***

Immediate release levodopa-carbidopa pellets (4:1) were prepared in accordance with the method described in Example 51. The weight and composition of pellets are given in Table 14A. Levodopa and carbidopa were blended with inactive excipients for 15 min. The levodopa-carbidopa-excipients blend was then granulated by spraying purified water while mixing at low shear. The granulation was blended for an additional 5 min and then extruded through a 1.0 mm screen of a Caleva extruder, model 25, operating at 10 rpm. The extrudate was spheronized in a Caleva spheronizer, model 250, operating at 1000 rpm for 5 min. The spheronized pellets were dried in a Vector MFL.01 Micro Batch Fluid Bed System at 50 °C for 120 min. The dried pellets were screened and particles with diameters ranging from 0.7 mm to 1.4 mm were selected for future experimentation.

Table 14A. Weight and Composition of Immediate Release Levodopa-Carbidopa Pellets, Lot # 603-069

Ingredients	**Weight %**	**Weight (g)**
Levodopa, USP	49.44	75.00
Carbidopa monohydrate, USP	13.49	20.46
Microcrystalline cellulose (EMCOCEL® 90 M), NF	14.83	22.50
Croscarmellose sodium (AC-DI-SOL®), NF	9.88	15.00
Anhydrous citric acid, USP	7.91	12.00
Polyethylene oxide (POLYOX™ WSR N10), NF	4.35	6.60
Butylated hydroxytoluene (BHT), NF	0.10	0.15
Total	100.00	151.71

Aliquots of screened pellets were encapsulated in 00-size hard gelatin capsules.

The *in vitro* dissolution profile of levodopa-carbidopa capsules, containing 200 mg levodopa and 50 mg carbidopa anhydrous was obtained under simulated gastric conditions. The dissolution test was performed in 900 mL of 0.1 N HCl - pH 1.2 solution in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution medium were collected at predetermined intervals and analyzed by online UV spectrophotometry. The combined dissolution profile of levodopa-carbidopa obtained from UV analysis is shown in Figure 83.

Example 77 ***Production and In vitro Dissolution of Immediate Release Levodopa-Carbidopa (10:1) Pellets, Lot # 602-033***

Immediate release levodopa-carbidopa pellets (10:1) were prepared in accordance with the method described in Example 51. The weight and composition of pellets are given in Table 15A. Levodopa and carbidopa were blended with inactive excipients for 15 min. The levodopa-carbidopa-excipients blend was then granulated by spraying purified water while mixing at low shear. The granulation was blended for an additional 5 min and then extruded through a 1.5 mm screen of a Caleva extruder, model 25, operating at 10 rpm. The extrudate was spheronized in a Caleva spheronizer, model 250, operating at 1000 rpm for 5 min. The spheronized pellets were dried in a Vector MFL.01 Micro Batch Fluid Bed System at 50 °C for 60 min. The dried pellets were screened and particles with diameters ranging from 1.0 mm to 2.0 mm were selected for future experimentation.

Table 15A. Weight and Composition of Immediate Release Levodopa-Carbidopa Pellets, Lot # 602-033

Ingredients	**Weight %**	**Weight (g)**
Levodopa, USP	54.73	82.50
Carbidopa monohydrate, USP	5.97	9.00
Microcrystalline cellulose (EMCOCEL® 90 M),	14.92	22.50
L-Glutamic acid, FCC	9.95	15.00
Croscarmellose sodium (AC-DI-SOL®), NF	9.95	15.00
Polyethylene oxide (POLYOX™ WSR N10), NF	4.38	6.60
Butylated hydroxytoluene (BHT), NF	0.10	0.15
Total	100.00	150.75

Aliquots of screened pellets were encapsulated in 000-size hard gelatin capsules. The *in vitro* dissolution profile of levodopa-carbidopa capsules, containing 200 mg levodopa and 50 mg carbidopa anhydrous was obtained under simulated gastric conditions. The dissolution test was performed in 900 mL of 0.1 N HCl - pH 1.2 solution in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution medium were collected at predetermined intervals and analyzed by online UV spectrophotometry. The combined dissolution profile of levodopa-carbidopa obtained from

UV analysis is shown in Figure 84.

Example 78 ***Production and in vitro Dissolution of Levodopa Pellets Prepared with Granulation-Extrusion-Spheronization and Low Concentration of Microcrystalline Cellulose, Lot # 510-048***

Levodopa pellets were prepared in accordance with the method described in Example 51. The weight and composition of pellets are given in Table 16A. Levodopa was blended with inactive excipients for 5 min. The levodopa-excipients blend was then granulated by spraying purified water while mixing at low shear. The granulation was extruded through a 1.5 mm screen of a Caleva extruder, model 25, operating at 15 rpm. The extrudate was spheronized in a Caleva spheronizer, model 250, operating at 1000 rpm for 5 min. The spheronized pellets were dried in a Precision oven at 50 °C overnight. The dried pellets were screened and particles with diameters ranging from 1.0 mm to 2.0 mm were selected for future experimentation.

Table 16A. Weight and Composition of Levodopa Pellets, Lot # 510-048

Ingredients	**Weight %**	**Weight (g)**
Mannitol (MANNOGEM™ Powdered), USP	59.0	118
Levodopa, USP	30.0	60
Microcrystalline cellulose (EMCOCEL® 90 M), NF	10.0	20
Anhydrous citric acid, USP	1.0	2
Total	100.0	200

Aliquots of screened pellets were encapsulated in 000-size hard gelatin capsules. The *in vitro* dissolution profile of levodopa capsules, containing 200 mg levodopa was obtained under simulated gastric conditions. The dissolution test was performed in 900 mL of 0.1N HCl - pH 1.2 solution in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution medium were collected at predetermined intervals and analyzed by online UV spectrophotometry. The dissolution profile of levodopa obtained from UV analysis is shown in Figure 85.

Example 79 ***Production and in vitro Dissolution of Levodopa Pellets Prepared with***

Granulation-Extrusion-Spheronization and Spheromer™ III, Lot # 511-045

Levodopa pellets were prepared in accordance with the method described in Example 51. The weight and composition of pellets are given in Table 17A. Levodopa was blended with inactive excipients for 5 min. The levodopa-excipients blend was then granulated by spraying purified water while mixing at low shear. The granulation was extruded through a 1.5 mm screen of a Caleva extruder, model 25, operating at 15 rpm. The extrudate was spheronized in a Caleva spheronizer, model 250, operating at 1250 rpm for 5 min. The spheronized pellets were dried in a Precision oven at 50 °C overnight. The dried pellets were screened and particles with diameters ranging from 1.0 mm to 2.0 mm were selected for future experimentation.

Table 17A. Weight and Composition of Levodopa Pellets, Lot # 511-045

Ingredients	**Weight %**	**Weight (g)**
Levodopa, USP	40.0	60.0
SPHEROMER™ III	30.0	45.0
Microcrystalline cellulose (EMCOCEL® 90 M), NF	28.0	42.0
Anhydrous citric acid, USP	2.0	3.0
Total	100.0	150.0

Aliquots of screened pellets were encapsulated in 00-size hard gelatin capsules.

The *in vitro* dissolution profile of levodopa capsules, containing 200 mg levodopa was obtained under simulated gastric conditions. The dissolution test was performed in 900 mL of 0.1N HCl - pH 1.2 solution in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution medium were collected at predetermined intervals and analyzed by online UV spectrophotometry. The dissolution profile of levodopa obtained from UV analysis is shown in Figure 86.

Example 80 ***Production and in vitro Dissolution of Levodopa Pellets Prepared with Granulation-Extrusion-Spheronization and Spheromer™ III, Lot # 512-085***

Levodopa pellets were prepared in accordance with the method described in

Example 51. The weight and composition of pellets are given in Table 18A. Levodopa was blended with inactive excipients for 5 min. The levodopa-excipients blend was then granulated by spraying a 5% (w/v) calcium chloride solution in water while mixing at low shear. About two-third of the granulation was extruded through a 1.5 mm screen of a Caleva extruder, model 25, operating at 15 rpm. The remaining part of the granulation was extruded through a 2.0 mm screen. The extrudate was spheronized in a Caleva spheronizer, model 250, operating at 1250 rpm for 5 min. The spheronized pellets were dried in a Precision oven at 50 °C overnight. The dried pellets were screened and particles with diameters ranging from 1.0 mm to 2.0 mm were selected for future experimentation.

Table 18A. Weight and Composition of Levodopa Pellets, Lot # 512-085

Ingredients	**Weight %**	**Weight (g)**
Levodopa, USP	38.86	60.0
SPHEROMER™ III	29.15	45.0
Microcrystalline cellulose (EMCOCEL® 90 M),	27.20	42.0
Calcium chloride, anhydrous, FCC	2.85	4.4
Anhydrous Citric Acid, USP	1.94	3.0
Total	100.00	154.4

Aliquots of screened pellets were encapsulated in 00-size hard gelatin capsules.

The *in vitro* dissolution profile of levodopa capsules, containing 200 mg levodopa was obtained under simulated gastric conditions. The dissolution test was performed in 900 mL of 0.1N HCl - pH 1.2 solution in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution medium were collected at predetermined intervals and analyzed by online UV spectrophotometry. The dissolution profile of levodopa obtained from UV analysis is shown in Figure 87.

Example 81 ***Production and in vitro Dissolution of Levodopa Pellets Prepared with Granulation-Extrusion-Spheronization and Glyceryl Monostearate, Lot # 601-002***

Levodopa pellets were prepared in accordance with the method described in Example 51. The weight and composition of pellets are given in Table 19A. Levodopa was

blended with inactive excipients for 5 min. The levodopa-excipients blend was then granulated by spraying purified water while mixing at low shear. The granulation was extruded through a 1.0 mm screen of a Caleva extruder, model 25, operating at 15 rpm. The extrudate was spheronized in a Caleva spheronizer, model 250, operating at 1000 rpm for 2.5 min, 1250 rpm for 1.5 min, and 1450 rpm for 1 min. The spheronized pellets were dried in a Precision oven at 50 °C overnight. The dried pellets were screened and particles with diameters ranging from 1.0 mm to 2.0 mm were selected for future experimentation.

Table 19A. Weight and Composition of Levodopa Pellets, Lot # 601-002

Ingredients	**Weight %**	**Weight (g)**
Levodopa, USP	50.0	75.0
Glyceryl monostearate, Powder, Food Grade	40.0	60.0
Anhydrous citric acid, USP	10.0	15.0
Total	100.0	150.0

Aliquots of screened pellets were encapsulated in 00-size hard gelatin capsules. The *in vitro* dissolution profile of levodopa capsules, containing 200 mg levodopa was obtained under simulated gastric conditions. The dissolution test was performed in 900 mL of 0.1N HCl - pH 1.2 solution in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution medium were collected at predetermined intervals and analyzed by online UV spectrophotometry. The dissolution profile of levodopa obtained from UV analysis is shown in Figure 88.

Example 82 ***Production and in vitro Dissolution of Immediate Release Carbidopa Pellets, Lot # 601-012***

Immediate release carbidopa pellets were prepared in accordance with the method described in Example 51. The weight and composition of pellets are given in Table 20A. Carbidopa was blended with inactive excipients for 10 min. The carbidopa-excipients blend was then granulated by spraying absolute ethanol while mixing at low shear. The granulation was blended for an additional 5 min and then extruded through a 1.5 mm screen of a Caleva extruder, model 25, operating at 15 rpm. The extrudate was spheronized in a Caleva spheronizer, model 250, operating at 1000 rpm for 5 min. The spheronized pellets

were dried in a Precision oven at 50°C for 60 min. The dried pellets were screened and particles with diameters ranging from 1.0 mm to 2.0 mm were selected for future experimentation.

Table 20A. Weight and Composition of Immediate Release Carbidopa Pellets, Lot # 601-012

Ingredients	Weight %	Weight (g)
Carbidopa monohydrate, USP	51.92	81.00
Microcrystalline cellulose (EMCOCEL® 90 M), NF	19.23	30.00
Anhydrous citric acid, USP	19.23	30.00
Croscarmellose sodium (AC-DI-SOL®), NF	5.77	9.00
Hydroxypropylcellulose (KLUCEL® EXF Pharm), NF	2.89	4.50
Ethylenediamine tetracetic acid	0.48	0.75
Sodium meta-bisulfite	0.48	0.75
Total	100.00	156.00

Aliquots of screened pellets were encapsulated in 00-size hard gelatin capsules.

The *in vitro* dissolution profile of carbidopa capsules, containing 200 mg carbidopa anhydrous was obtained under simulated gastric conditions. The dissolution test was performed in 900 mL of 0.1N HCl - pH 1.2 solution in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution medium were collected at predetermined intervals and analyzed by online UV spectrophotometry. The dissolution profile of carbidopa obtained from UV analysis is shown in Figure 89.

Example 83 ***Production and in vitro Dissolution of Levodopa Pellets Prepared with Granulation-Extrusion-Spheronization and Low Concentration of Microcrystalline Cellulose, Lot # 602-001***

Levodopa pellets were prepared in accordance with the method described in Example 51. The weight and composition of pellets are given in Table 21A. Levodopa was blended with inactive excipients for 10 min. The levodopa-excipients blend was then granulated by spraying purified water while mixing at low shear. The granulation was extruded through a 1.5 mm screen of a Caleva extruder, model 25, operating at 10 rpm. The

extrudate was spheronized in a Caleva spheronizer, model 250, operating at 1000 rpm for 5 min. The spheronized pellets were dried in a Vector MFL.01 Micro Batch Fluid Bed System at 50 °C for 60 min. The dried pellets were screened and particles with diameters ranging from 1.0 mm to 2.0 mm were selected for future experimentation.

Table 21A. Weight and Composition of Levodopa Pellets, Lot # 602-001

Ingredients	Weight %	Weight (g)
Levodopa, USP	78.95	120.0
L-Glutamic acid hydrochloride, FCC	9.87	15.0
Microcrystalline cellulose (EMCOCEL® 90 M), NF	6.25	9.5
Hydroxypropylcellulose (L-HPC LH-31)	4.93	7.5
Total	100.0	152.0

Aliquots of screened pellets were encapsulated in 00-size hard gelatin capsules.

The *in vitro* dissolution profile of levodopa capsules, containing 200 mg levodopa was obtained under simulated gastric conditions. The dissolution test was performed in 900 mL of 0.1N HCl - pH 1.2 solution in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution medium were collected at predetermined intervals and analyzed by online UV spectrophotometry. The dissolution profile of levodopa obtained from UV analysis is shown in Figure 90.

Example 84 ***Production and in vitro Dissolution of Immediate Release Levodopa Pellets Prepared with Granulation-Extrusion-Spheronization and Low Concentration of Microcrystalline Cellulose, Lot # 602-024***

Levodopa pellets were prepared in accordance with the method described in Example 51. The weight and composition of pellets are given in Table 22A. Levodopa was blended with inactive excipients for 10 min. The levodopa-excipients blend was then granulated by spraying purified water while mixing at low shear. The granulation was extruded through a 1.5 mm screen of a Caleva extruder, model 25, operating at 10 rpm. The extrudate was spheronized in a Caleva spheronizer, model 250, operating at 1000 rpm for 5 min. The spheronized pellets were dried in a Vector MFL.01 Micro Batch Fluid Bed System at 50 °C for 150 min. The dried pellets were screened and particles with diameters ranging

from 1.0 mm to 2.0 mm were selected for future experimentation.

Table 22A. Weight and Composition of Levodopa Pellets, Lot # 602-024

Ingredients	**Weight %**	**Weight (g)**
Levodopa, USP	54.28	82.5
Co-processed Starch (STARCAP 1500™) *	24.67	37.5
Microcrystalline cellulose (EMCOCEL® 90 M), NF	11.18	17.0
L-Glutamic acid hydrochloride, FCC	9.87	15.0
Total	100.0	152.0

* STARCAP 1500™ is a co-processed mixture of corn starch and pregelatinized starch.

Aliquots of screened pellets were encapsulated in 00-size hard gelatin capsules.

The *in vitro* dissolution profile of levodopa capsules, containing 200 mg levodopa was obtained under simulated gastric conditions. The dissolution test was performed in 900 mL of 0.1N HCl - pH 1.2 solution in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution medium were collected at predetermined intervals and analyzed by online UV spectrophotometry. The dissolution profile of levodopa obtained from UV analysis is shown in Figure 91.

Example 85 ***Production and in vitro Dissolution of Immediate Release Levodopa Pellets Prepared with Granulation-Extrusion-Spheronization and Co-processed Starch, Lot # 602-028***

Levodopa pellets were prepared in accordance with the method described in Example 51. The weight and composition of pellets are given in Table 23A. Levodopa was blended with inactive excipients for 10 min. The levodopa-excipients blend was then granulated by spraying purified water while mixing at low shear. The granulation was extruded through a 1.5 mm screen of a Caleva extruder, model 25, operating at 10 rpm. The extrudate was spheronized in a Caleva spheronizer, model 250, operating at 1000 rpm for 5 min. The spheronized pellets were dried in a Vector MFL.01 Micro Batch Fluid Bed System at 50°C for 95 min. The dried pellets were screened and particles with diameters ranging

from 1.0 mm to 2.0 mm were selected for future experimentation.

Table 23A. Weight and Composition of Levodopa Pellets, Lot # 602-024

Ingredients	Weight %	Weight (g)
Levodopa, USP	53.22	82.5
Co-processed Starch (STARCAP 1500™)	37.10	57.5
L-Glutamic acid hydrochloride, FCC	9.68	15.0
Total	100.0	155.0

* STARCAP 1500™ is a co-processed mixture of corn starch and pregelatinized starch.

Aliquots of screened pellets were encapsulated in 00-size hard gelatin capsules. The *in vitro* dissolution profile of levodopa capsules, containing 200 mg levodopa was obtained under simulated gastric conditions. The dissolution test was performed in 900 mL of 0.1N HCl - pH 1.2 solution in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution medium were collected at predetermined intervals and analyzed by online UV spectrophotometry. The dissolution profile of levodopa obtained from UV analysis is shown in Figure 92.

Example 86 ***Preparation of Pramipexole Extended-Release Pellet Formulation, Lot # 601-048***

An extended-release pellet formulation of pramipexole was prepared to be combined with an immediate- and controlled-release multiparticulate formulation of levodopa-carbidopa. Pramipexole was initially layered on placebo core pellets (1.1– 1.4 mm dia.) with OPADRY® Clear as a binder using a Vector MFL.01 Micro Batch Fluid Bed System, equipped with a Wurster insert.

The placebo core pellets were prepared using low-shear granulation, extrusion and spheronization technique. Table 24A provides the weight and composition of placebo core pellets.

Table 24A. Weight and Composition of Placebo Core Pellets

Ingredients	Weight (%)	Weight (g)
Microcrystalline Cellulose (Emcocel® 90M), NF	30.0	60.0
Mannitol (Mannogem™ Powdered), USP	65.0	130.0
Hydroxypropylcellulose (HPC-SSL), NF	5.0	10.0
Purified Water, USP	*	*
Total	100.0	200.0

* Evaporated during drying process.

The placebo pellets were dried in an oven at 50 °C to achieve a desired moisture level of 1% (w/w). These pellets were then screened through size 10, 12, 14, 16 and 18 mesh sieves and the particles retained on screen size 14 and 16 were used for subsequent pramipexole layering process.

Pramipexole layered pellets were subsequently coated in the Vector MFL.01 Micro Batch Fluid Bed System, equipped with a Wurster insert, with a release rate-controlling polymer composition containing ethylcellulose to achieve a weight gain of 8.3% (w/w), and then coated with bioadhesive SPHEROMER™ III polymer to a weight gain of 5.3% (w/w).

The unit dose composition of a pramipexole 0.375 mg extended-release pellet formulation is given in Table 25A.

Table 25A. Unit Dose Composition of Pramipexole 0.375 mg Extended-Release Pellet Formulation

Components	Weight (%)	Weight (mg)
Pramipexole Dihydrochloride Monohydrate, USP	0.33	0.375
Mannitol (MANNOGEM™ Powdered), USP	53.44	60.93
Microcrystalline Cellulose (EMCOCEL® 90M), NF	24.67	28.13
Ethylcellulose (ETHOCEL™ Std 10 FP Premium), NF	7.26	8.28
OPADRY® Clear (YS-1-19025-A)	4.94	5.63

SPHEROMER™ III	4.78	5.45
Hydroxypropyl Cellulose (HPC-SSL), NF	4.11	4.69
Poloxamer 188 (LUTROL® F 68), NF	0.25	0.29
Dibutyl Sebacate, NF	0.22	0.25
Total	100.00	114.025

The bioadhesive pramipexole pellets may be optionally top-coated with bioadhesive SPHEROMER™ I polymer, a hyprolmellose polymer, a hydroxypropylcellulose polymer, or a polyvinyl alcohol polymer to a weight gain of 2-5% (w/w).

Example 87 ***Preparation of Combined Pramipexole 0.375 mg Extended-Release Pellets and Levodopa-Carbidopa 200 mg/50 mg Immediate/Controlled-Release Multiparticulates as a Delayed-Release Capsule Formulation***

Pramipexole extended-release pellets, lot # 601-048 (from Example 86), containing 0.375 mg pramipexole, and levodopa-carbidopa immediate/controlled-release multiparticulates, lot # 510-099 (from Example 71), containing 200 mg levodopa and 50 mg carbidopa, were co-encapsulated in two-piece hard gelatin capsules. These capsules were sealed at the junction of cap and body using an aqueous gelatin solution and then coated with 1.6% (w/w) OPADRY® Clear (YS-1-19025-A). The Opadry-coated capsules were top-coated with an enteric coating composition, ACRYL-EZE™ White, in a pan coater (O'Hara Technologies Labcoat System). The capsules were sprayed with a 10% (w/v) solution of ACRYL-EZE™ White in ethanol and water mixture (90:10 v/v) so as to achieve a final weight gain of 5-12% (w/w).

The bioadhesive pramipexole and levodopa-carbidopa pellets may be optionally top-coated with bioadhesive SPHEROMER™ I polymer, a hyprolmellose polymer, a hydroxy-propylcellulose polymer, or a polyvinyl alcohol polymer to a weight gain of 2-5% (w/w).

Example 88 ***Preparation of Pramipexole 0.375 mg Delayed/Extended-Release Capsule Formulation, Lot # 601-056***

Pramipexole extended-release pellets, lot # 601-048 (from Example 86), containing 0.375 mg pramipexole were encapsulated in a size 2 hard shell gelatin capsule. These capsules were sealed at the junction of cap and body using an aqueous gelatin solution and

coated with 1.6 % OPADRY® Clear (YS-1-19025-A). The OPADRY-coated capsules were then coated with an enteric coating composition, ACRYL-EZE™ White, in a pan coater (O'Hara Technologies Labcoat System). The capsules were sprayed with a 10% (w/v) solution of ACRYL-EZE™ White in ethanol and water mixture (90:10 v/v) so as to achieve a final weight gain of 5-12% (w/w).

The unit dose composition of a pramipexole 0.375 mg delayed/extended-release capsule formulation is given in Table 26A.

Table 26A. Unit Dose Composition of Pramipexole 0.375 mg Delayed/Extended-Release Capsule Formulation

Components	**Weight (%)**	**Weight (mg)**
Pramipexole Dihydrochloride Monohydrate, USP	0.13	0.375
Mannitol (MANNOGEM™ Powdered), USP	21.45	60.93
Microcrystalline Cellulose (EMCOCEL® 90M), NF	9.90	28.13
ACRYL-EZE™ White (93O18509)	8.14	23.12
OPADRY® Clear (YS-1-19025-A)	3.13	8.90
Ethylcellulose (ETHOCEL™ Std 10 FP Premium), NF	2.91	8.28
SPHEROMER™ III	1.81	5.14
Hydroxypropyl Cellulose (HPC-SSL), NF	1.65	4.69
Poloxamer 188 (LUTROL® F 68), NF	0.10	0.27
Dibutyl Sebacate, NF	0.09	0.25
Gelatin Capsule, Size 2	50.69	144.00
Total	100.00	284.085

Example 89 ***Preparation of Combined Pramipexole 0.375 mg Delayed/Extended-Release Pellets and Levodopa-Carbidopa 200 mg/50 mg Immediate/Controlled-Release Multiparticulates as a Capsule Formulation***

Pramipexole delayed/extended-release pellets, lot # 601-056 (from Example 88), containing 0.375 mg pramipexole, and levodopa-carbidopa immediate-controlled-release

multiparticulates, lot # 510-099 (from Example 71), containing 200 mg levodopa and 50 mg carbidopa, were co-encapsulated in two-piece hard gelatin capsules.

The bioadhesive pramipexole and levodopa-carbidopa pellets may be optionally top-coated with bioadhesive SPHEROMER™ I polymer, a hyprolmellose polymer, a hydroxy-propylcellulose polymer, or a polyvinyl alcohol polymer to a weight gain of 2-5% (w/w).

A multiparticulate capsule formulation of levodopa-carbidopa 200 mg/50 mg comprising carbidopa granules, levodopa pellets, and bioadhesive SPHEROMER™ IV-coated levodopa-carbidopa pellets was prepared, and its *in vivo* pharmacokinetic performance was compared with that of a marketed controlled-release formulation, SINEMET® CR 50-200, in fed beagle dogs.

In the following, Examples 90 to 94 describe the methods of preparation of levodopa-carbidopa multiparticulate capsules. Examples 95 and 96 present the *in vitro* dissolution and *in vivo* pharmacokinetic performance of levodopa-carbidopa multiparticulate capsules and SINEMET® CR 50-200 tablets, repectively.

Example 90 ***Production of Carbidopa Granules with Low Shear Granulation, Lot # 508-081***

Carbidopa granules were produced with low shear granulation method comprising the following processes:

(1) Weighing carbidopa and LUDIPRESS®, a co-processed mixture of povidone (3.5%), crospovidone (3.5%), and lactose monohydrate (93.0%).

(2) Blending carbidopa and LUDIPRESS® from step (1) in a planetary type mixer, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5 min, forming a dry mix.

(3) Granulating the dry mix from step (2) under low shear with a 5% (w/v) aqueous solution of povidone, forming a wet granulation.

(4) Drying the granulation from step (3) to the moisture content of 0.8% in a conventional Precision oven at 50 °C.

(5) Screening and classifying the dried granules from step (4) through a stack of stainless steel sieves, U.S. standard mesh sizes 20 and 60, using a mechanical sieve shaker, W.S. Tyler Sieve Shaker Ro-Tap Rx-29, operated for 5 min. Particle size and distribution of granular formulations were analyzed, and classified

granules ranging from 0.25 mm (mesh # 60) to 0.85 mm (mesh # 20) were selected for future experimentation.

The dry weight and composition of granules are given in Table 90-1.

Table 90-1. Dry Weight and Composition of Carbidopa Granules, Lot # 508-081

Ingredients	Weight %	Weight (g)
Carbidopa monohydrate, USP	24.7	50.0
LUDIPRESS		
Povidone, USP	2.6	5.3
Crospovidone, USP	2.6	5.3
Lactose Monohydrate, Ph Eur	68.9	139.4
Povidone (PLASDONE® K-25), USP	1.2	2.4
Total	100.0	202.4

Example 91 ***Production of Levodopa Pellets with Granulation-Extrusion-Spheronization, Lot # 509-053***

Levodopa pellets were produced with granulation-extrusion-spheronization method comprising the following processes:

(1) Weighing levodopa and pharmaceutically acceptable excipients.

(2) Blending levodopa and excipients from step (1) in a planetary type mixer, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5 min, forming a dry mix.

(3) Granulating the dry mix from step (2) under low shear with purified water, forming a wet granulation.

(4) Extruding the wet granulation from step (3) through the screen of a screen-type extruder, Caleva Model 25 Extruder, operating at 15 rpm, and forming breakable wet strands, the extrudate. The screen aperture was 1.5 mm.

(5) Spheronizing the extrudate from step (4) in a spheronizer, Caleva Model 250, equipped with a 2.5-mm spheronization plate, operating at 1250 rpm for 5 min, and forming spheronized pellets.

(6) Drying the spheronized pellets from step (5) to the moisture content of 0.4% in a conventional Precision oven at 50 °C.

(7) Screening and classifying the dried pellets from step (6) through a stack of stainless steel sieves, U.S. standard mesh sizes 10, 12, 14, 16, and 18 using a mechanical sieve shaker, W.S. Tyler Sieve Shaker Ro-Tap Rx-29, operated for 5 min. Particle size and distribution of pellet formulations were analyzed, and classified pellets ranging from 1.0 mm (mesh # 18) to 2.0 mm (mesh # 10) were selected for future experimentation.

The dry weight and composition of pellets are given in Table 91-1.

Table 91-1. Dry Weight and Composition of Levodopa Pellets, Lot # 509-053

Ingredients	**Weight %**	**Weight (g)**
Levodopa, USP	50.0	200.0
Microcrystalline cellulose (EMCOCEL® 90 M), NF	25.0	100.0
Mannitol (MANNOGEM™ Powdered), USP	14.0	56.0
Hydroxypropylcellulose (HPC-SSL), NF	5.0	20.0
Croscarmellose sodium (AC-DI-SOL®), NF	5.0	20.0
Citric acid, anhydrous, USP	1.0	4.0
Total	100.0	400.0

Example 92 ***Production of Levodopa-Carbidopa (4:1) Pellets with Granulation-Extrusion-Spheronization, Lot # 512-062***

Levodopa-carbidopa pellets were produced with granulation-extrusion-spheronization method comprising the following processes:

(1) Weighing levodopa, carbidopa, and pharmaceutically acceptable excipients.

(2) Blending levodopa, carbidopa, and excipients from step (1) in a planetary type mixer, Hobart Mixer with a 5-qt mixing bowl, operating at the speed setting #1, for 5 min, forming a dry mix.

(3) Granulating the dry mix from step (2) under low shear with purified water, forming a wet granulation.

(4) Extruding the wet granulation from step (3) through the screen of a screen-type extruder, Caleva Model 25 Extruder, operating at 15 rpm, and forming breakable wet strands, the extrudate. The screen aperture was 1.5 mm.

(5) Spheronizing the extrudate from step (4) in a spheronizer, Caleva Model 250, equipped with a 2.5-mm spheronization plate, operating at 1000 rpm for 5 min, and forming spheronized pellets.

(6) Drying the spheronized pellets from step (5) to the moisture content of 1% in a conventional Precision oven at 50 °C.

(7) Screening and classifying the dried pellets from step (6) through a stack of stainless steel sieves, U.S. standard mesh sizes 10, 12, 14, 16, and 18 using a mechanical sieve shaker, W.S. Tyler Sieve Shaker Ro-Tap Rx-29, operated for 5 min. Particle size and distribution of pellet formulations were analyzed, and classified pellets ranging from 1.0 mm (mesh # 18) to 2.0 mm (mesh # 10) were selected for future experimentation.

The dry weight and composition of pellets are given in Table 92-1.

Table 92-1. Dry Weight and Composition of Levodopa-Carbidopa Pellets, Lot # 512-062

Ingredients	**Weight %**	**Weight (g)**
Levodopa, USP	48.3	100.0
Carbidopa monohydrate, USP	13.0	27.0
Microcrystalline cellulose (EMCOCEL® 90 M), NF	26.6	55.0
Crospovidone (POLYPLASDONE® XL), USP	5.8	12.0
Povidone (PLASDONE® K-25), USP	3.4	7.0
Citric acid, anhydrous, USP	2.9	6.0
Total	100.0	207.0

Example 93 ***Film coating of Levodopa-Carbidopa Pellets with Bioadhesive Polymer, SPHEROMER™ IV, Lot # 601-004***

Fifty grams of levodopa-carbidopa pellets, lot # 512-062, were film-coated with bioadhesive SPHEROMER™ IV polymer in a Vector MFL.01 Micro Batch Fluid Bed System, equipped with a Wurster insert. The fluid bed system was operated at inlet air flow rate of 100 lpm (liter per minute) and temperature of 35-40°C. The composition of the

coating solution is given in Table 80-1. SPHEROMER™ IV and Poloxamer 188 (LUTROL® F68) were dissolved in a mixture of methyl alcohol and water and sprayed onto the fluidized pellets to obtain a 6% weight gain on pellets.

Table 93-1. Composition of Spheromer™ IV Coating Solution, Lot # 601-004

Ingredients	Weight %	Weight (g)
SPHEOROMER™ IV	95	2.90
Poloxamer 188 (LUTROL® F68), NF	5	0.15
Methyl alcohol, NF	*	(75 mL)
Purified Water, HPLC Grade	*	(25 mL)
Total Solids	100	3.05

* Methyl alcohol and water were removed during the coating/drying process.

Example 94 ***Preparation of Levodopa-Carbidopa 200 mg/50 mg Multiparticulate Capsules, Lot # 601-038***

Carbidopa granules (lot # 508-081), levodopa pellets (lot # 509-053), and SPHEROMER™ IV-coated levodopa-carbidopa pellets (lot # 601-004) were encapsulated in 00-size hard gelatin capsules. Each capsule contained 200 mg levodopa and 50 mg carbidopa anhydrous. The composition of encapsulated multiparticulates is given in Table 94-1.

Table 94-1. Composition (mg) of Multiparticulate Capsule Formulations, Lot # 601-038

Components	Lot #	Wt. (mg)
Carbidopa Granules	508-081	40
Levodopa Pellets	509-053	80
SPHEROMER™ IV-coated Levodopa-Carbidopa Pellets	510-098	348
Total (mg per capsule)	-	468

Example 95 ***In vitro Dissolution and in vivo Pharmacokinetic Performance of***

Levodopa-Carbidopa 200 mg/50 mg Multiparticulate Capsules, Lot # 601-038

The *in vitro* dissolution profile of levodopa-carbidopa capsules, containing 200 mg levodopa and 50 mg carbidopa was obtained under simulated gastric conditions. The dissolution tests were performed in 900 mL of 0.1N HCl – pH 1.2 solution in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of dissolution media were collected at predetermined intervals and analyzed by HPLC. The dissolution profiles of levodopa and carbidopa obtained from HPLC analysis are shown in Figure 93.

The *in vivo* performance of levodopa-carbidopa capsules was evaluated in beagle dogs. The capsules were administered to separate cohorts of twelve beagle dogs in the fed state. Plasma levels of levodopa and carbidopa were measured using LC/MS/MS analysis. Figures 94 and 95 show the plasma concentration profiles of levodopa and carbidopa in the fed state, respectively. The pharmacokinetic data including the area under the plasma levodopa vs. time curve (AUC), max. concentration (C_{max}) and time required to achieve C_{max} (T_{max}) are provided in Table 95-1.

Table 95-1. Pharmacokinetic Data for Levodopa-Carbidopa Multiparticulate Capsules, Lot # 601-038, in Fed Beagle Dogs; the area under the plasma levodopa vs. time curve (AUC), maximum concentration (C_{max}), and time required to achieve C_{max} (T_{max})

Fasting Period	AUC (ng/ml.hr)	C_{max} (ng/ml)	T_{max} (hr)
Fed State	9,649	1,615	3.8

Example 96 ***In vitro Dissolution and in vivo Pharmacokinetic Performance of SINEMET® CR 50-200 Tablets, containing 50 mg Carbidopa and 200 mg Levodopa, Lot # N4682***

The *in vitro* dissolution profile of SINEMET® CR 50-200 tablets, containing 50 mg carbidopa and 200 mg levodopa were obtained under simulated gastric conditions. The dissolution tests were performed in 900 mL of 0.1N HCl - pH 1.2 solution, in a USP II apparatus at a temperature of 37 °C. The paddle speed was set at 50 rpm. Samples of

dissolution media were collected at predetermined intervals and analyzed by HPLC. The dissolution profiles of levodopa and carbidopa obtained from HPLC analysis are shown in Figure 96.

The *in vivo* pharmacokinetic performance of SINEMET® CR 50-200 tablets was evaluated in beagle dogs. SINEMET® CR tablets were administered to cohorts of six beagle dogs in the fed state and plasma levels of levodopa and carbidopa were measured using HPLC analysis. Figures 94 and 95 show the plasma concentration profiles of levodopa and carbidopa. The pharmacokinetic data including the area under the plasma levodopa vs. time curve (AUC), maximum concentration (C_{max}) and time required to achieve C_{max} (T_{max}) are provided in Table 96-1.

Table 96-1. Pharmacokinetic Data for SINEMET® CR 50-200 Tablets, Lot # N4682, in Fed Beagle Dogs; the area under the plasma levodopa vs. time curve (AUC), maximum concentration (C_{max}), and time required to achieve C_{max} (T_{max})

Formulation	AUC (ng/ml.hr)	C_{max} (ng/ml)	T_{max} (hr)
SINEMET® CR 50-200 Tablets	3,903	1,663	2

Equivalents:

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

All patents, publications, and other references cited above are hereby incorporated by reference in their entirety.

We Claim:

1. A pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising:

(1) a first immediate-release (IR) portion comprising levodopa or a metabolic precursor thereof, formulated to provide a therapeutically effective concentration of levodopa or the precursor in the patient within about 2 hours of administration to the patient; and

(2) a second portion comprising levodopa or a metabolic precursor thereof, formulated to release levodopa or the precursor at a substantially zero-order release rate over a sustained treatment period to maintain the therapeutically effective concentration of levodopa or the precursor in the patient;

wherein at least the first IR portion further comprises a decarboxylase enzyme inhibitor, and the ratio of the inhibitor to levodopa or the precursor in at least the first IR portion is greater than 1:4.

2. The pharmaceutical composition of claim 1, further comprising:

(3) a substantially ascending release portion comprising levodopa or a metabolic precursor thereof, formulated to effect a rapid drop of levodopa concentration in the patient to below the therapeutically effective concentration at the end of the treatment period.

3. The pharmaceutical composition of claim 1, further comprising:

(3) a substantially elevating release portion comprising levodopa or a metabolic precursor thereof, formulated to elevate the substantially zero-order release rate to a higher level beginning around a predetermined time point.

4. The pharmaceutical composition of claim 3, wherein the predetermined time point is about four to seven hours after administration to the patient.

5. The pharmaceutical composition of claim 3, wherein the substantially elevating release portion is formulated to effect a rapid drop of levodopa concentration in the patient to below the therapeutically effective concentration at the end of the treatment period.

6. The pharmaceutical composition of claim 3, wherein the substantially elevating

release portion comprises a decarboxylase enzyme inhibitor.

7. A pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising:

(1) a first immediate-release (IR) portion comprising levodopa or a metabolic precursor thereof, formulated to provide a therapeutically effective concentration of levodopa in the patient within about 2 hours of administration to the patient;

(2) a second portion comprising levodopa or a metabolic precursor thereof, formulated to release levodopa or the precursor at a substantially zero-order release rate over a sustained treatment period to maintain the therapeutically effective concentration of levodopa in the patient; and

(3) a substantially ascending release portion comprising levodopa or a metabolic precursor thereof, formulated to effect a rapid drop of levodopa concentration in the patient to below the therapeutically effective concentration at the end of the treatment period.

8. A pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising:

(1) a first immediate-release (IR) portion comprising levodopa or a metabolic precursor thereof, formulated to provide a therapeutically effective concentration of levodopa in the patient within about 2 hours of administration to the patient;

(2) a second portion comprising levodopa or a metabolic precursor thereof, formulated to release levodopa or the precursor at a substantially zero-order release rate over a sustained treatment period to maintain the therapeutically effective concentration of levodopa in the patient; and

(3) a substantially elevating release portion comprising levodopa or a metabolic precursor thereof, formulated to elevate the substantially zero-order release rate to a higher level beginning at a predetermined time point.

9. A pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising:

(1) a sleep-inducing agent; and,

(2) a decarboxylase enzyme inhibitor formulated to provide an effective plasma

concentration at a predetermined time after the administration of the pharmaceutical composition to the patient.

10. The pharmaceutical composition of claim 9, further comprising:

(3) a first delayed immediate-release (DIR) portion comprising levodopa or a metabolic precursor thereof, formulated to provide a therapeutically effective concentration of levodopa in the patient within about 2 hours of the predetermined time.

11. The pharmaceutical composition of claim 10, further comprising:

(4) a second delayed controlled release (DCR) portion comprising levodopa or a metabolic precursor thereof, formulated to release levodopa or the precursor at a substantially zero-order release rate over a sustained treatment period after the predetermined time, to maintain the therapeutically effective concentration of levodopa in the patient.

12. The pharmaceutical composition of claim 10, wherein the predetermined time after administration is 6 to 9 hours after administration.

13. The pharmaceutical composition of claim 2, 5, or 7, where the rapid drop of levodopa takes place in less than two hours.

14. The pharmaceutical composition of any of claims 1-13, wherein the formulation further comprises one or more of: a dopaminergic and anti-cholinergic agent selected from: amantadine; an anti-cholinergic agent selected from: trihexyphenidyl, benztropine, ethoproprazine, or procyclidine; a dopamine agonist selected from: apomorphine, bromocriptine, cabergoline, lisuride, pergolide, pramipexole, or ropinirole; a MAO-B (monoamine oxidase B) inhibitor selected from: selegiline or deprenyl; a COMT inhibitor selected from: CGP-28014, entacapone, or tolcapone; a muscle relaxant baclofen; a sedative Clonazepam; an anticonvulsant agent carbamazepine; a dopamine reuptake inhibitor tetrabenazine; a dopamine blocker haloperidol; a β-blocker selected from: propranolol; a carbonic anhydrase inhibitor selected from: acetalzolamide or methazolamide; a narcotic agent codeine; a GABAergic agent gabapentin; or an alpha antagonist clonidine.

15. The pharmaceutical composition of any of claims 1-14, wherein the formulation further comprises a stool softener selected from: bran or psyllium, methylcellulose, polycarbophil, docusate, docusate sodium and casanthranol combination,

magnesium hydroxide, magnesium citrate, sorbitol, polyethylene glycol solution, lactulose, lubiprostone or other osmotic or stimulant laxatives, and a natural stool softener.

16. The pharmaceutical composition of any of claims 1-15, wherein the metabolic precursor is a methyl, ethyl, or propyl ester of levodopa, or a combination thereof.

17. The pharmaceutical composition of any of claims 1-15, wherein the metabolic precursor is (−)-L-α-amino-β-(3,4-dihydroxybenzene) propanoic acid, 3-hydroxy-L-tyrosine ethyl ester, phenylglycine, or a mixture thereof.

18. The pharmaceutical composition of any of claims 1-17, wherein the ratio of the decarboxylase inhibitor to levodopa or the precursor in the first IR portion is about 1:3 or greater.

19. The pharmaceutical composition of any of claims 1-17, wherein the ratio of the decarboxylase inhibitor to levodopa or its precursor varies between the start and the end of the release of the second portion.

20. The pharmaceutical composition of claim 19, wherein the ratio changes substantially continuously over the release period of the second portion.

21. The pharmaceutical composition of claim 19, wherein the ratio is substantially constant during all or a part of the release period of the second portion.

22. The pharmaceutical composition of claim 2, 3, 7, or 8, wherein the substantially ascending release portion or the substantially elevating release portion comprises a decarboxylase enzyme inhibitor.

23. The pharmaceutical composition of claim 2, 3, 7, or 8, wherein the substantially ascending release portion or the substantially elevating release portion is a second immediate release portion.

24. The pharmaceutical composition of any of claims 2-23, wherein the ratio of the inhibitor to levodopa or the precursor in the substantially ascending release portion or the substantially elevating release portion is less than 1:4.

25. The pharmaceutical composition of any of the preceding claims, wherein the decarboxylase enzyme inhibitor is carbidopa, a carbidopa prodrug, benserazide, methylphenidate, or a combination thereof.

26. The pharmaceutical composition of any of the preceding claims, wherein the total dose of the decarboxylase enzyme inhibitor per day per human patient is in the range

of about 75 – 600 mg.

27. The pharmaceutical composition of any of the preceding claims, wherein the total dose of levodopa or metabolic precursor thereof per day per human patient is between about 50 mg and about 300 mg.

28. The pharmaceutical composition of any of the preceding claims, wherein at least one of the first IR portion, the second substantially zero order release portion, the substantially elevating release portion, and/or the substantially ascending release portion further comprises at least one dopamine transport inhibitor.

29. The pharmaceutical composition of claim 28, wherein the dopamine transport inhibitor is methylphenidate.

30. The pharmaceutical composition of claim 28, wherein the dopamine transport inhibitor is present in an amount of about 3 mg to about 60 mg.

31. The pharmaceutical composition of claim 28, wherein the dopamine transport inhibitor is released starting after a delay of about 2 hours to about 7 hours.

32. The pharmaceutical composition of claim 31, wherein the dopamine transport inhibitor is released over a period of time of about 1 hour to about 6 hours.

33. The pharmaceutical composition of any one of the claims 1-32, wherein the first IR portion, the second substantially zero order release portion, the substantially elevating release portion (if present), and the substantially ascending release portion (if present), are formulated to provide a sustained dose over at least 4 hours when administered to the patient.

34. The pharmaceutical composition of claim 33, wherein the first IR portion, the second substantially zero order release portion, the substantially elevating release portion, and the substantially ascending release portion (if present), are formulated to provide a sustained dose over at least 8 hours when administered to the patient.

35. The pharmaceutical composition of claim 34, wherein the first IR portion, the second substantially zero order release portion, the substantially elevating release portion (if present), and the substantially ascending release portion (if present), are formulated to provide a sustained dose over at least 12 hours when administered to the patient.

36. The pharmaceutical composition of claim 35, wherein the first IR portion, the second substantially zero order release portion, the substantially elevating release

portion (if present), and the substantially ascending release portion (if present), are formulated to provide a sustained dose over at least 14 hours when administered to the patient.

37. The pharmaceutical composition of any one of the claims 1-36, wherein the first IR portion, the second substantially zero order release portion, the substantially elevating release portion (if present), and the substantially ascending release portion (if present), are formulated into a stack of compressed inserts encased inside a shell, each portion having an independent dissolution profile, wherein drug is released only from an exposed surface at a predetermined face of the stack.

38. The pharmaceutical composition of any one of the claims 1-36, wherein the first IR portion, the second substantially zero order release portion, the substantially elevating release portion (if present), and the substantially ascending release portion (if present), are each formulated as a plurality of individual beads or pellets, each of the portions having an independent dissolution profile.

39. The pharmaceutical composition of claim 38, wherein the ratio of beads corresponding to the first IR portion, the second substantially zero order release portion, and the substantially ascending release portion (if present), are customized for the patient to provide a predetermined release profile selected from: a predetermined duration of release, a predetermined rate of reaching a therapeutic plasma concentration of levodopa, or a predetermined maximum release rate customized for the size, sensitivity, or clearance rate of the particular patient.

40. The pharmaceutical composition of claim 39, wherein some or all of the beads are fully or partially coated by a bioadhesive material.

41. The pharmaceutical composition of claim 40, wherein the beads of the second substantially zero order release and third substantially elevating or substantially ascending release portions (if present), are coated by a bioadhesive material.

42. The pharmaceutical composition of any of claims 38-41, wherein some or all of the beads are coated by a dispersion-promoting coating.

43. The pharmaceutical composition of any of claims 38-42, wherein the beads are less than about 1 mm in diameter.

44. The pharmaceutical composition of any of claims 38-43, wherein the beads are dispersed in a matrix that disintegrates in less than about 5 minutes.

45. The pharmaceutical composition of any of claims 38-43, wherein the beads are dispersed in an eroding tablet that gradually erodes over the treatment period.

46. The pharmaceutical composition of claim 45, wherein the tablet is at least partially coated by a bioadhesive material and/or an immediate release portion.

47. The pharmaceutical composition of claim 46, wherein the bioadhesive material, if present, is exposed upon dissolution of the immediate release portion.

48. The pharmaceutical composition of claim 37, wherein the shell is fully or partially coated by a bioadhesive material.

49. The pharmaceutical composition of any of the preceding claims, wherein at least the substantially zero-order release rate second portion is coated or partially coated by a bioadhesive material.

50. The pharmaceutical composition of any of claims 40-49, wherein the bioadhesive material is selected from polyamides, polyalkylene glycols, polyalkylene oxides, polyvinyl alcohols, polyvinylpyrrolidone, polyglycolides, polyurethanes, polymers of acrylic and methacrylic esters, polylactides, poly(butyric acid), polyanhydrides, polyorthoesters, poly(fumaric) anhydride, blends and copolymers thereof.

51. The pharmaceutical composition of any of claims 40-49, wherein the bioadhesive material is poly(fumaric-co-sebacic) anhydride.

52. The pharmaceutical composition of any of claims 40-49, wherein the bioadhesive material comprises a catechol moiety.

53. The pharmaceutical composition of claim 52, wherein the bioadhesive material comprises a mixture of a material and a compound comprising a catechol moiety selected from L-Dopa, D-dopa, dopamine, or carbidopa.

54. The pharmaceutical composition of claim 52 or 53, wherein the bioadhesive material is selected from polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polyglycolides, polysiloxanes, polyurethanes, polystyrene, polymers of acrylic and methacrylic esters, polylactides, poly(butyric acid), poly(valeric acid), poly(lactide-co-glycolide), polyanhydrides, polyorthoesters, poly(fumaric) anhydride, blends, and/or copolymers thereof.

55. The pharmaceutical composition of any of claims 40-49, wherein the bioadhesive

material is covalently functionalized with a catechol moiety.

56. The pharmaceutical composition of claim 55, wherein the catechol moiety is derived from L-dopa, D-dopa, dopamine, or carbidopa.

57. The pharmaceutical composition of any of the preceding claims, formulated for oral administration.

58. The pharmaceutical composition of any of claims 1-56, formulated for parenteral administration.

59. The pharmaceutical composition of any of the preceding claims, suitable for human treatment, or for veterinary treatment of a non-human mammal.

60. The pharmaceutical composition of any of the preceding claims, wherein the first IR portion is liquid.

61. The pharmaceutical composition of any of the preceding claims, wherein the first IR portion, the second substantially zero order release portion, the substantially elevating release portion (if present), and the substantially ascending release portion (if present), are suspended in a pharmaceutically acceptable liquid carrier.

62. A method of making a pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising combining the first IR portion, the second portion, the substantially elevating release portion (if present), and the substantially ascending release portion (if present), of any of the pharmaceutical composition of claims 1-60 into a single dosage form.

63. A method of treating a patient suffering from Parkinson's disease and/or another movement disorder, comprising administering to the patient a pharmaceutical composition of any of claims 1-61.

64. A method of treating a patient suffering from Parkinson's disease and/or another movement disorder, comprising administering to the patient the pharmaceutical composition of claim 1, conjointly with a substantially ascending release portion comprising levodopa or precursor thereof formulated to effect a rapid drop of levodopa concentration in the patient to below the therapeutically effective concentration at the end of the treatment period, when the release of the pharmaceutical composition of claim 1 is or is about to be completed in the patient.

65. A pharmaceutical preparation of any of claims 1-60 formulated as a transdermal patch, a buccal patch, or a buccal tablet, and formulated for sustained release of the

pharmaceutical composition in order to administer an amount sufficient to treat a patient suffering from Parkinson's disease and/or another movement disorder, wherein said pharmaceutical composition is formulated to provide a sustained substantial zero-order release over at least 8 hours after applying to the patient.

66. A single dosage formulation for treatment of a movement disorder comprising levodopa or a metabolic precursor thereof, wherein the dosage formulation produces and maintains a therapeutically effective concentration of levodopa or precursor thereof over a period of at least about 7 hours.

67. The single dosage formulation of claim 66, further comprising a decarboxylase enzyme inhibitor.

68. The single dosage formulation of claim 66 or 67, wherein the dosage formulation produces and maintains a therapeutically effective concentration of levodopa or precursor thereof over a period of at least about 9 hours.

69. The single dosage formulation of claim 68, wherein the dosage formulation produces and maintains a therapeutically effective concentration of levodopa or precursor thereof over a period of at least about 12 hours.

70. The single dosage formulation of any of claims 66-69, wherein the dosage formulation includes a first immediate-release (IR) portion to attain a therapeutically effective concentration of said levodopa in less than about 2 hours after administration to a patient.

71. The single dosage formulation of claim 70, which further comprises:

(1) a sustained zero-order release portion to maintain the therapeutically effective concentration of levodopa over a first period of hours; and

(2) an ascending-release portion to maintain the therapeutically effective concentration of levodopa at the end of said sustained zero-order release portion;

wherein the single dosage formulation, upon administration to the patient, produces a therapeutically effective concentration of said levodopa or precursor in less than about 2 hours of administration to a patient.

72. The single dosage formulation of claim 71, wherein the ascending release portion provides for a rate of decrease of levodopa in the patient from a therapeutically effective concentration to a sub-therapeutically effective concentration (*e.g.*, < 75%

or less) in a second period of time less than about 2 hours.

73. The single dosage formulation of any of claims 67-72, wherein the ratio of the inhibitor to levodopa or the precursor in at least the first IR portion is greater than 1:4.

74. The single dosage formulation of any of claims 70-73, wherein the decarboxylase enzyme inhibitor is present in only the first IR portion and the sustained zero-order release portion.

75. The single dosage formulation of any of claims 70-73, wherein the decarboxylase enzyme inhibitor is present in each of the portions, wherein the ratio of decarboxylase enzyme inhibitor to levodopa in each portion is different.

76. The single dosage formulation of any of claims 71-75, wherein the sustained zero-order release portion comprises two or more sub-portions differing in the ratio of decarboxylase enzyme inhibitor to levodopa or the precursor.

77. The single dosage formulation of any of claims 71-75, wherein at least one of the first IR portion, the second substantially zero order release portion, and the substantially ascending release portion further comprises at least one dopamine transport inhibitor.

78. The single dosage formulation of any of claims 71-75, wherein the second substantially zero order release portion and/or the substantially ascending release portion further comprises a bioadhesive material.

79. The pharmaceutical composition of claim 40, wherein the bioadhesive material comprises an additive that stabilizes the material from erosion, dissolution or both, wherein at least 50% by weight of a 1 mm thick film of the bioadhesive material remains after 12 hours in a buffered pH 4.5 dissolution bath.

80. The pharmaceutical composition of claim 40, wherein the bioadhesive material comprises an additive selected from one or more of a polyanhydride, an acidic component, a metal compound, a stabilizing polymer and a hydrophobic component.

81. A packaged pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising:

(1) a first pharmaceutical composition comprising the pharmaceutical composition of claim 1, 2, or 3;

(2) a second pharmaceutical composition comprising the pharmaceutical

composition of claim 9, 10, or 11.

82. The packaged pharmaceutical composition of claim 81, wherein the first and/or the second pharmaceutical composition is packaged separately as individual doses.

83. The packaged pharmaceutical composition of claim 82, wherein the package comprises at least one dose each of the first and the second pharmaceutical compositions.

84. The packaged pharmaceutical composition of claims 81-83, wherein the first and the second pharmaceutical compositions are distinctively marked by color, shape, and/or size.

85. The packaged pharmaceutical composition of claims 81-84, further comprising an instruction that instructs a patient to take the first pharmaceutical composition as a day dose, and to take the second pharmaceutical composition as a night dose.

86. The packaged pharmaceutical composition of claims 81-85, which package comprises sufficient doses for treating a patient over a week.

87. A multiparticulate pharmaceutical composition, comprising:

(1) a plurality of pellets, each said pellets comprising a core comprising one or more effective ingredients; and

(2) a matrix material;

wherein the pellets are dispersed in the matrix material, and are released upon dissolution of the matrix material.

88. The pharmaceutical composition of claim 87, wherein the matrix material disintegrates within about 5 minutes in an aqueous solution.

89. The pharmaceutical composition of claim 88, wherein the aqueous solution is gastric acid.

90. The pharmaceutical composition of claim 88, wherein the matrix material comprises a cushioning material.

91. The pharmaceutical composition of claim 87, wherein the pharmaceutical composition is an eroding tablet and the matrix material gradually erodes over a predetermined period of time.

92. The pharmaceutical composition of claim 91, wherein the eroding tablet is at least partially coated by a support material or a bioadhesive material.

93. The pharmaceutical composition of claim 87, wherein the plurality of pellets comprise two or more different types of pellets.

94. The pharmaceutical composition of claim 93, wherein a first type of pellets further comprise one or more coatings around the core of each pellet.

95. The pharmaceutical composition of claim 94, wherein the coatings comprise a bioadhesive composition, a composition for controlled-release, a composition for delayed-release, a dispersion-promoting composition, and/or a functional or non-functional polymer.

96. The pharmaceutical composition of claim 95, wherein the different coatings, if present, are in two or more discrete layers.

97. The pharmaceutical composition of claim 96, wherein the layers comprise a controlled-release layer disposed around the core, a bioadhesive layer disposed around the controlled-release layer, and a dispersion-promoting layer disposed around the bioadhesive polymer layer.

98. The pharmaceutical composition of claim 95, wherein at least two different coatings are combined in the same coating layer.

99. The pharmaceutical composition of claim 94, wherein the effective ingredients comprise about 50-80% (v/v) of the coated pellets.

100. The pharmaceutical composition of claim 94, wherein the effective ingredients are at least about 60% (v/v) of the coated pellets, and the effective ingredients are cohesive, plastic, and engage in hydrogen bonding.

101. The pharmaceutical composition of any of claims 87, 99, and 100, wherein the pellets are no more than 1 mm in size.

102. The pharmaceutical composition of claim 94, wherein the core is substantially free of microcrystalline cellulose.

103. The pharmaceutical composition of claim 87, wherein the effective ingredient is one or more of: metformin, acyclovir, ranitidine, riboflavin, chlorthiazide, gabapentin, losartin potassium, ganciclovir, cimetidine, minocycline, fexofenadine, bupropion, orlistat, captopril, diphenhydramine, tripelennamine, chlorpheniramine maleate, promethazine, omeprazole, prostaglandin, carbenoxolane, sucralphate, isosorbide, quinidine, enalapril, nifedipine, verapamil, diltiazem, nadolol, timolol, pindolol, salbutamol, terbutaline, carbuterol, broxaterol, aminophylline, cyclizine, cinnarizine,

domperidone, alizapride, vincristine, megestrol acetate, daunorubicin, actinomycin, adriamycin, etoposide, 5-fluorouracil, indomethacin, sulindac, piroxicam, ibuprofen, naproxen, ketoprofen, temazepam, lorazepam, flunitrazepam, amantadine, ampicillin, amoxicillin, erythromycin, tetracyclines, cyanocobalamin, amino acids, iron or calcium salts of essential trace elements, or pharmacologically acceptable salts thereof.

104. A method to formulate a pharmaceutical composition, comprising:

(1) blending the pharmaceutical composition to form a dry mix;

(2) granulating the dry mix with a granulation fluid to form a wet granulation;

(3) extruding the wet granulation through a screen-type extruder to form extrudate;

(4) spheronizing the extrudate to form spheronized pellets; and

(5) drying the pellets.

105. The method of claim 104, wherein the pharmaceutical composition comprises two or more effective ingredients.

106. The method of claim 105, wherein the effective ingredients comprise levodopa and/or a metabolic precursor thereof, and a decarboxylase enzyme inhibitor.

107. The method of claim 104, wherein the pharmaceutical composition comprises a bioadhesive composition and/or a pharmaceutically acceptable excipient.

108. The method of claim 104, wherein the pharmaceutical composition is substantially free of microcrystalline cellulose.

109. The method of claim 104, wherein the granulation fluid is purified water, an aqueous solution of a mineral or organic acid, an aqueous solution of a polymeric composition, a pharmaceutically acceptable alcohol, a ketone or a chlorinated solvent, a hydro-alcoholic mixture, an alcoholic or hydro-alcoholic solution of a polymeric composition, or a solution of a polymeric composition in a chlorinated solvent or in a ketone.

110. The method of claim 104, wherein the extruder has a screen aperture of about 0.8, 1, or 1.5 mm.

111. The method of claim 104, further comprising:

(6) screening and/or classifying the pellets to select one or more pellets of a desired size.

112. The method of claim 111, wherein the selected pellets are no more than about 1 mm in diameter.

113. The method of claim 111, further comprising:

(7) coating the selected pellets with one or more coatings to form coated pellets.

114. The method of claim 113, wherein the coatings comprise a bioadhesive composition, a composition for controlled-release, a composition for delayed-release, a dispersion-promoting composition, and/or a functional or non-functional polymer.

115. The method of claim 114, wherein the different coatings, if present, are in discrete layers.

116. The method of claim 114, wherein at least two different coatings are combined in a single layer.

117. The method of claim 113, further comprising:

(8) dispersing the coated pellets in a matrix material that disintegrates within about 5 minutes in an aqueous solution.

118. The method of claim 117, wherein the aqueous solution is gastric acid.

119. The method of claim 117, wherein the matrix material comprises a cushioning material.

120. The method of claim 113, wherein the effective ingredient(s) of the pharmaceutical composition comprises about 50-80% (v/v) of the coated pellets.

121. The method of claim 113, further comprising:

(8) dispersing the coated pellets in a matrix of an eroding tablet that gradually erodes over a predetermined period of time.

122. The method of claim 121, wherein the eroding tablet is at least partially coated by a support material or a bioadhesive material.

123. Pellets formulated by the method of claim 104.

124. A method to formulate a pharmaceutical composition, comprising:

(1) blending the pharmaceutical composition to form a dry mix;

(2) granulating the dry mix under low shear condition with a granulation fluid to form a wet granulation;

(3) drying the wet granulation to form dried granulation;

(4) grinding the dried granulation, and sieving through a screen of predetermined

size to form sieved granules;

(5) blending in a lubricant to the sieved granules to form a uniformly lubricated dry mix.

125. The method of claim 124, wherein the pharmaceutical composition comprises two or more effective ingredients.

126. The method of claim 125, wherein the effective ingredients comprise levodopa and/or a metabolic precursor thereof, and a decarboxylase enzyme inhibitor.

127. The method of claim 124, wherein the pharmaceutical composition comprises a bioadhesive composition and/or a pharmaceutically acceptable excipient.

128. The method of claim 124, wherein the pharmaceutical composition is substantially free of microcrystalline cellulose.

129. The method of claim 124, wherein in step (1), the pharmaceutical composition is substantially free of lubricants.

130. The method of claim 124, wherein the granulation fluid is purified water, an aqueous solution of a mineral or organic acid, an aqueous solution of a polymeric composition, a pharmaceutically acceptable alcohol, a ketone or a chlorinated solvent, a hydro-alcoholic mixture, an alcoholic or hydro-alcoholic solution of a polymeric composition, or a solution of a polymeric composition in a chlorinated solvent or in a ketone.

131. The method of claim 124, further comprising:

(6) passing the lubricated dry mix through a second screen.

132. The method of claim 124, further comprising:

(6) compressing the lubricated dry mix into a tablet.

133. The method of claim 132, further comprising:

(6) film-coating the tablet with one or more coating compositions.

134. The method of claim 133, wherein the coating compositions comprise a bioadhesive composition, a composition for controlled-release, a composition for delayed-release, a dispersion-promoting composition, and/or a functional or non-functional polymer.

135. The method of claim 134, wherein the different coating compositions, if present, are in discrete layers.

136. The method of claim 134, wherein at least two different coating compositions are mixed in the same coating layer.

137. A pharmaceutical composition formulated with the method of claim 124.

138. A multiparticulate pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising:

(1) a first immediate-release (IR) portion comprising:

(a) a plurality of pellets comprising levodopa or a metabolic precursor thereof (levodopa pellets), and

(b) a plurality of pellets comprising carbidopa or a prodrug thereof (carbidopa pellets),

wherein said first IR portion is formulated to provide a therapeutically effective concentration of levodopa in the patient within about 30 minutes of administration to the patient, and

(2) a second portion comprising a plurality of pellets (levodopa-carbidopa pellets), each comprising:

(a) a first core comprising levodopa (or a metabolic precursor thereof) and carbidopa (or a prodrug thereof); and

(b) a bioadhesive composition coating the first core,

wherein said second portion is formulated to release levodopa at a substantially zero-order release rate over a sustained treatment period to maintain the therapeutically effective concentration of levodopa in the patient.

139. The pharmaceutical composition of claim 138, wherein the w/w ratio of carbidopa: levodopa is about 1:4 in the first and second portions.

140. The pharmaceutical composition of claim 138, wherein the second portion comprises about 80-90% of the levodopa in the pharmaceutical composition.

141. The pharmaceutical composition of claim 138, further comprising:

(3) a third portion comprising a plurality of pellets (levodopa-bioadhesive pellets), each comprising:

(a) a second core comprising levodopa (or a metabolic precursor thereof); and,

(b) a bioadhesive composition coating the second core,

wherein the second and third portions are formulated to release levodopa at a substantially zero-order release rate over a sustained treatment period to maintain the therapeutically effective concentration of levodopa in the patient.

142. The pharmaceutical composition of claim 141, wherein the second and third portions comprise about 80-90% of the levodopa in the pharmaceutical composition.

143. The pharmaceutical composition of claim 141 or 142, wherein the second portion comprises about 60-70% of the levodopa in the pharmaceutical composition.

144. The pharmaceutical composition of claim 141, wherein the levodopa pellets, the carbidopa pellets, the levodopa-carbidopa pellets, and the levodopa-bioadhesive pellets are all disposed in a capsule.

145. The pharmaceutical composition of claim 141, wherein the levodopa pellets, the carbidopa pellets, the levodopa-carbidopa pellets, and the levodopa-bioadhesive pellets are all dispersed in a matrix material that disintegrates within about 5 minutes in an aqueous solution.

146. The pharmaceutical composition of claim 145, wherein the matrix material comprises a cushioning material.

147. The pharmaceutical composition of claim 141, wherein the levodopa pellets, the carbidopa pellets, the levodopa-carbidopa pellets, and the levodopa-bioadhesive pellets are all dispersed in a matrix of an eroding tablet that gradually erodes over a predetermined period of time.

148. The pharmaceutical composition of claim 147, wherein the eroding tablet is at least partially coated by a support material or a bioadhesive material.

149. The pharmaceutical composition of claim 138 or 141, wherein the bioadhesive material coating the first and the second cores further comprises a dispersion-promoting agent.

150. The pharmaceutical composition of claim 138 or 141, wherein the levodopa pellets, the carbidopa pellets, the levodopa-carbidopa pellets, and the levodopa-bioadhesive pellets (if present) are no more than about 1 mm in size.

151. The pharmaceutical composition of claim 138 or 141, which is substantially free of microcrystalline cellulose.

152. The pharmaceutical composition of claim 138, wherein the bioadhesive material comprises an additive that stabilizes the material from erosion, dissolution or both,

wherein at least 50% by weight of a 1 mm thick film of the bioadhesive material remains after 12 hours in a buffered pH 4.5 dissolution bath.

153. The pharmaceutical composition of claim 138, wherein the bioadhesive material comprises an additive selected from one or more of a polyanhydride, an acidic component, a metal compound, a stabilizing polymer and a hydrophobic component.

154. A multilayer tablet pharmaceutical composition for the treatment of a patient suffering from Parkinson's disease and/or another movement disorder, comprising:

(1) a first controlled-release (CR) layer comprising levodopa (or a metabolic precursor thereof) and carbidopa (or a prodrug thereof), wherein the w/w ratio of carbidopa : levodopa is about 1:4 in the CR layer;

(2) a second, bioadhesive layer covering at least a portion of the first CR layer;

wherein the tablet is formulated to release levodopa at a substantially zero-order release rate over a sustained treatment period to maintain the therapeutically effective concentration of levodopa in the patient.

155. The multilayer tablet pharmaceutical composition of claim 154, further comprising:

(3) a third, immediate-release (IR) layer comprising levodopa (or a metabolic precursor thereof) and carbidopa (or a prodrug thereof), said third layer covering at least a portion of the first CR layer and/or the second bioadhesive layer, wherein the w/w ratio of carbidopa : levodopa is about 1:4 in the third IR layer.

156. The multilayer tablet pharmaceutical composition of claim 155, wherein the CR layer comprises about 80% of the total levodopa in the composition.

157. The multilayer tablet pharmaceutical composition of claim 155, further comprising:

(4) a fourth, pre-compressed immediate-release (IR) portion comprising levodopa (or a metabolic precursor thereof) and carbidopa (or a prodrug thereof), wherein said fourth portion is disposed within the CR layer, and wherein the w/w ratio of carbidopa : levodopa is about 1:4 in the fourth portion.

158. The multilayer tablet pharmaceutical composition of claim 157, wherein the fourth portion comprises about 15-25% of the total levodopa in the composition, and the CR layer comprises about 50-70% of the total levodopa in the composition.

FIG. 1

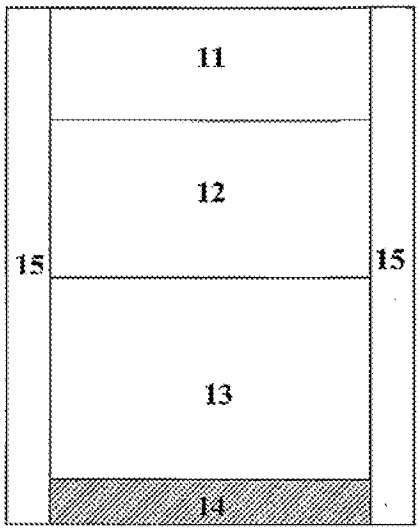


FIG. 2

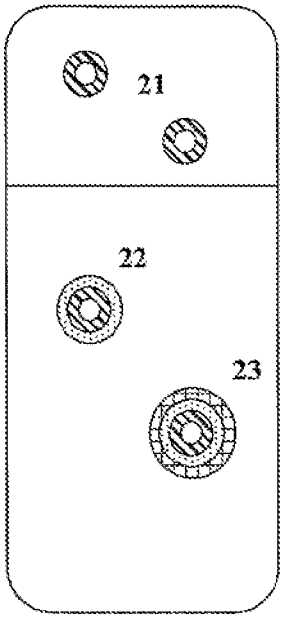


FIG. 3

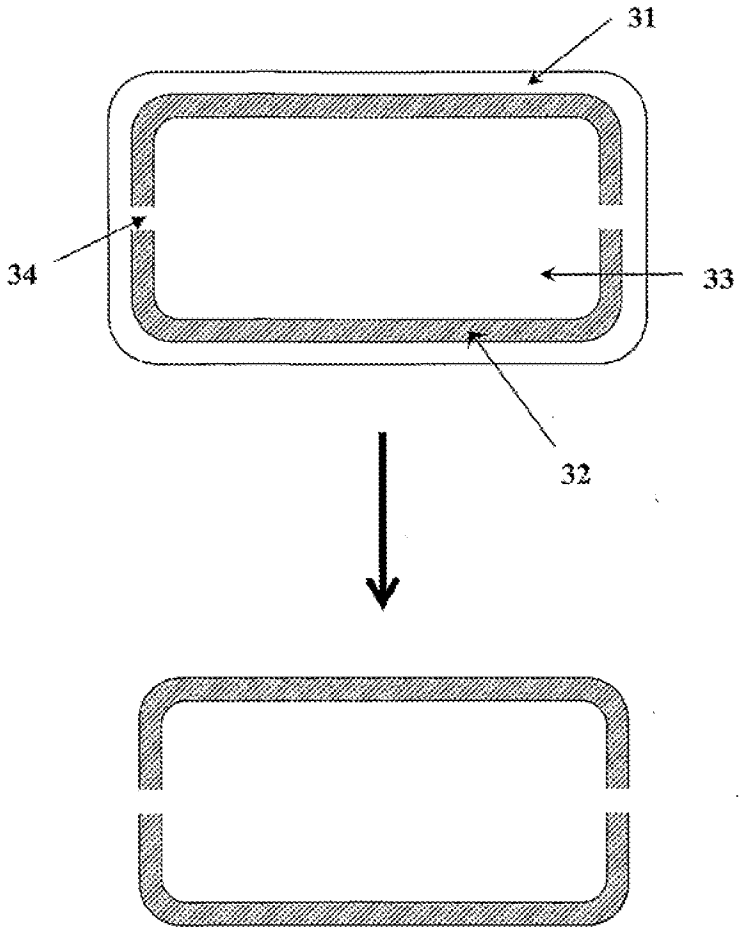


FIG. 4

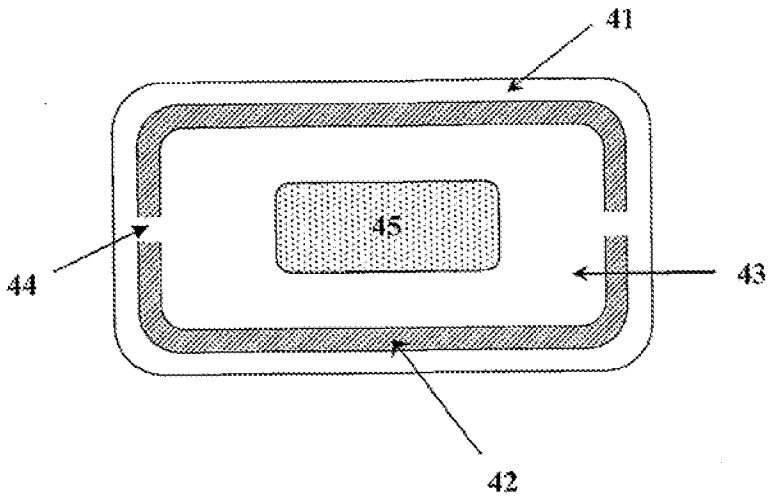


FIG. 5

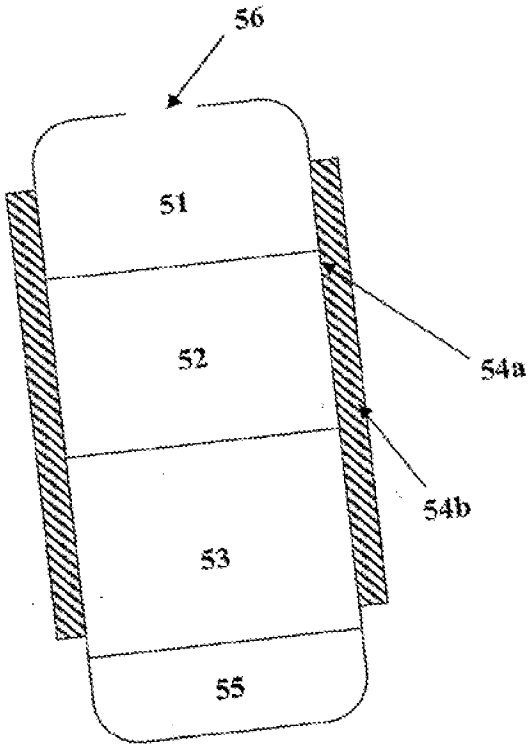


FIG. 6

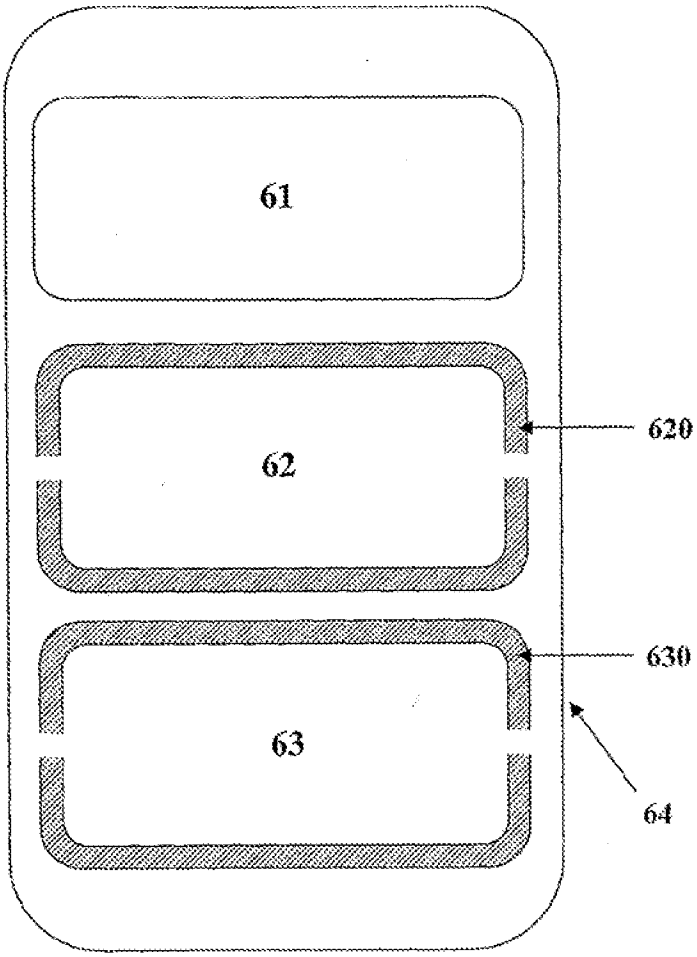


FIG. 7

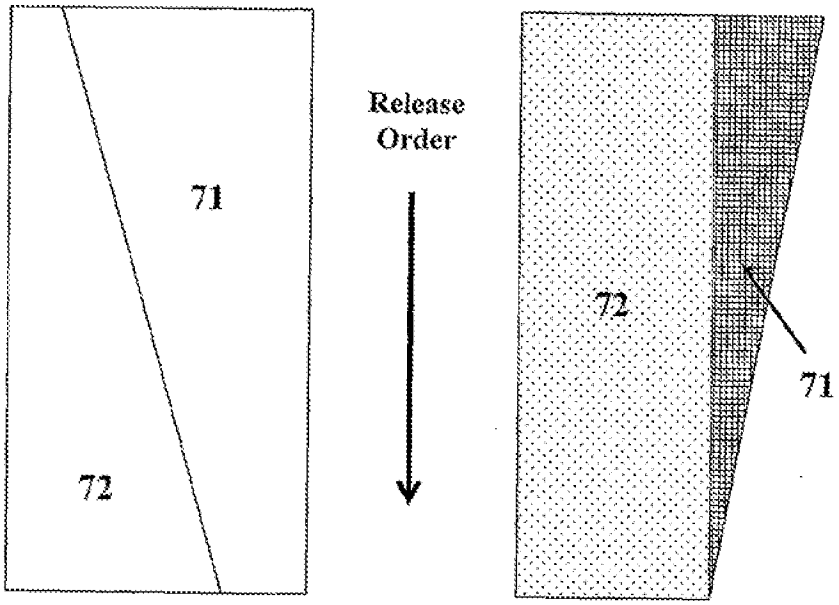


FIG. 8

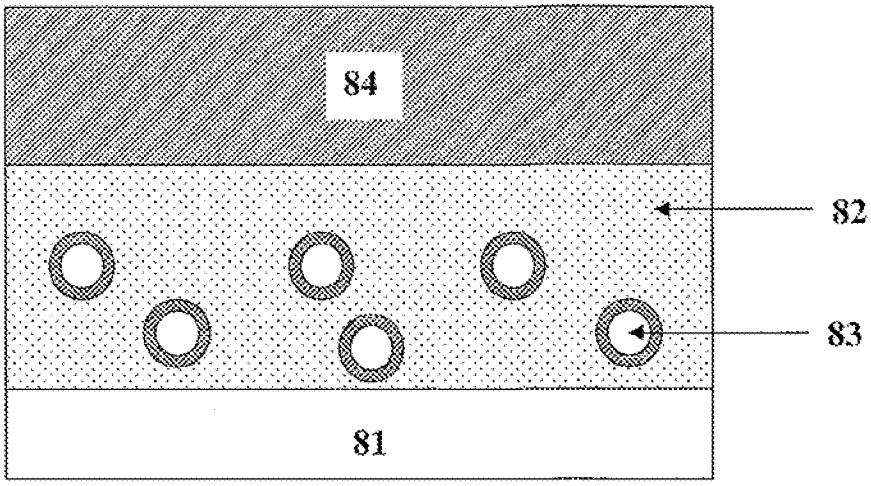


FIG. 9

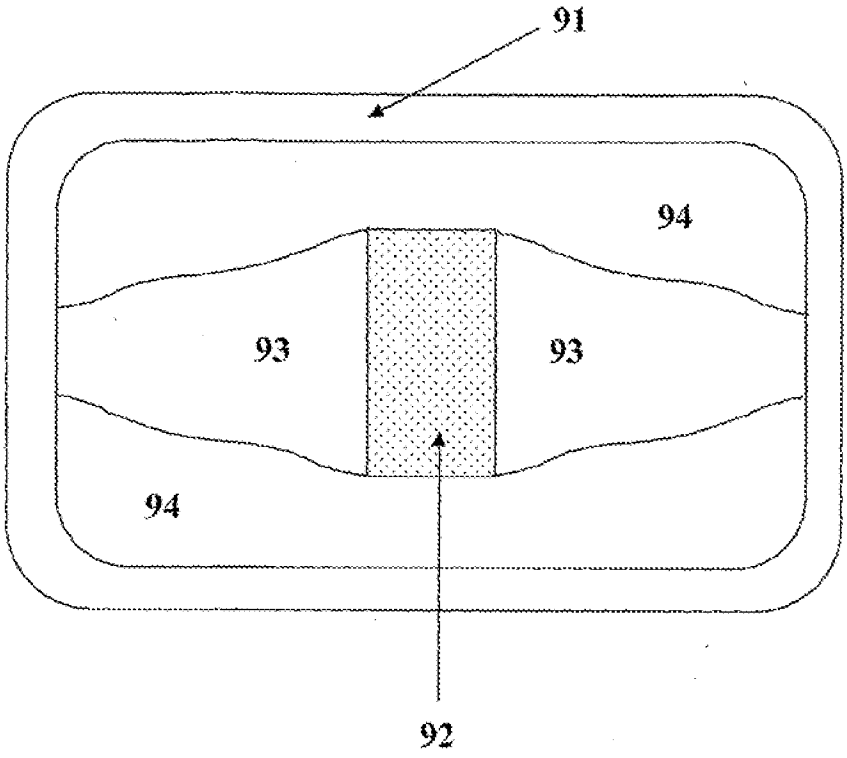


FIG. 10

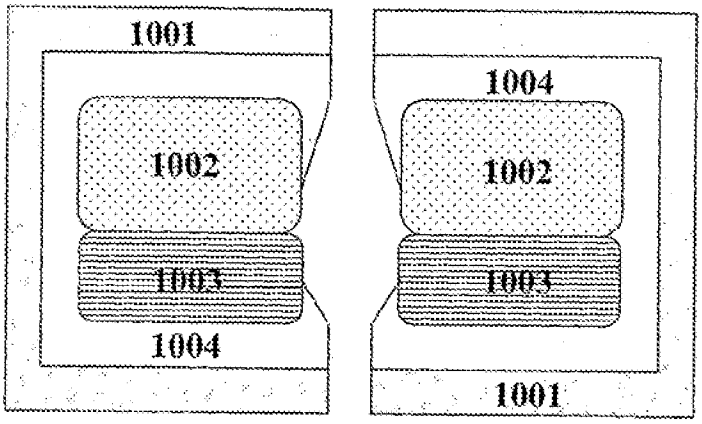


FIG. 11

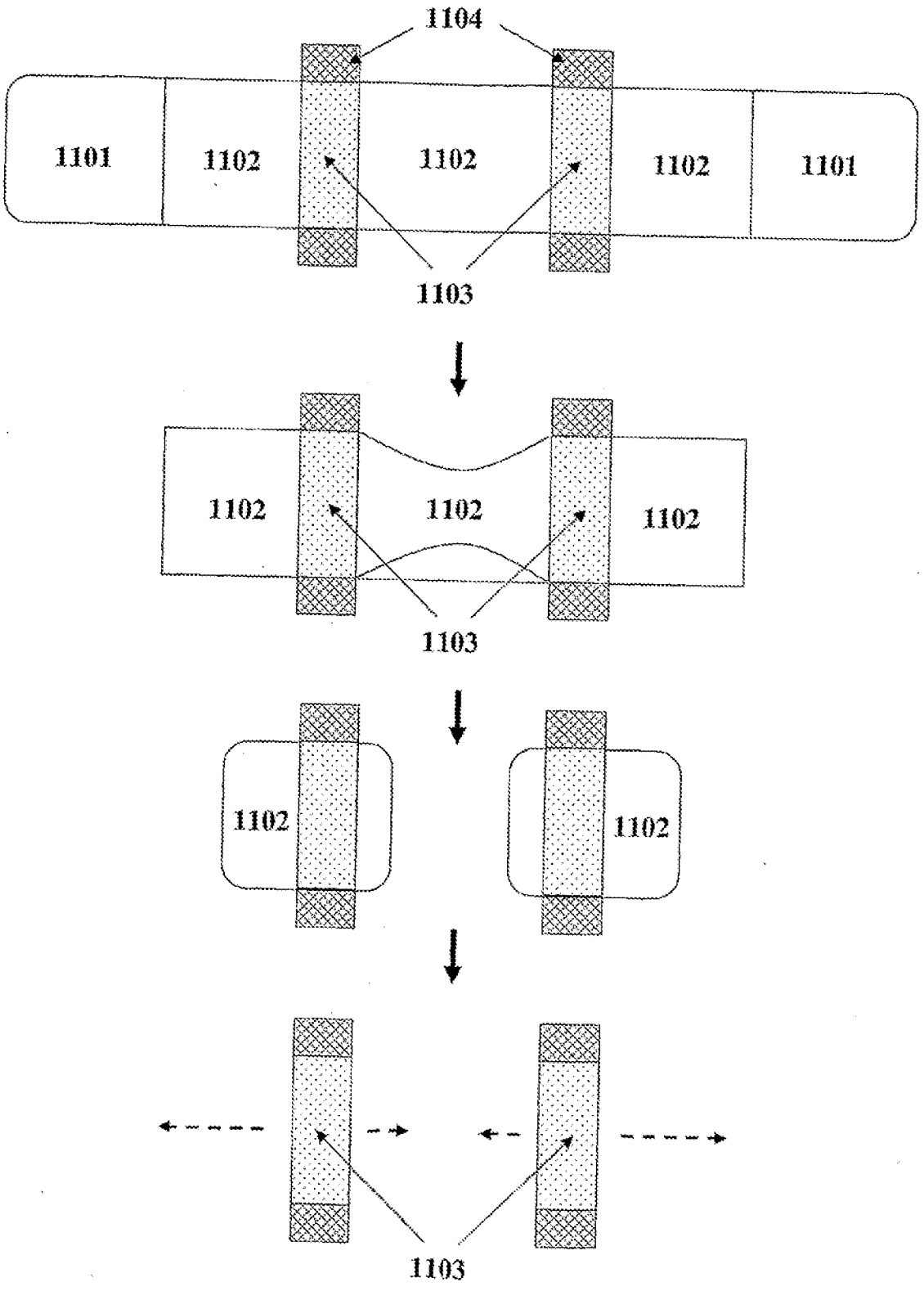

1104
1101
1102
1102
1102
1101
1103
1102
1102
1102
1103
1102
1102
1103

FIG. 12

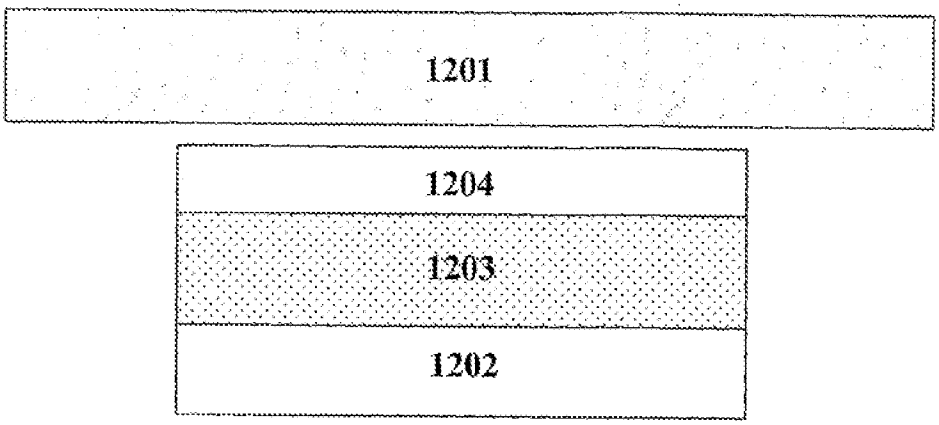


FIG. 13

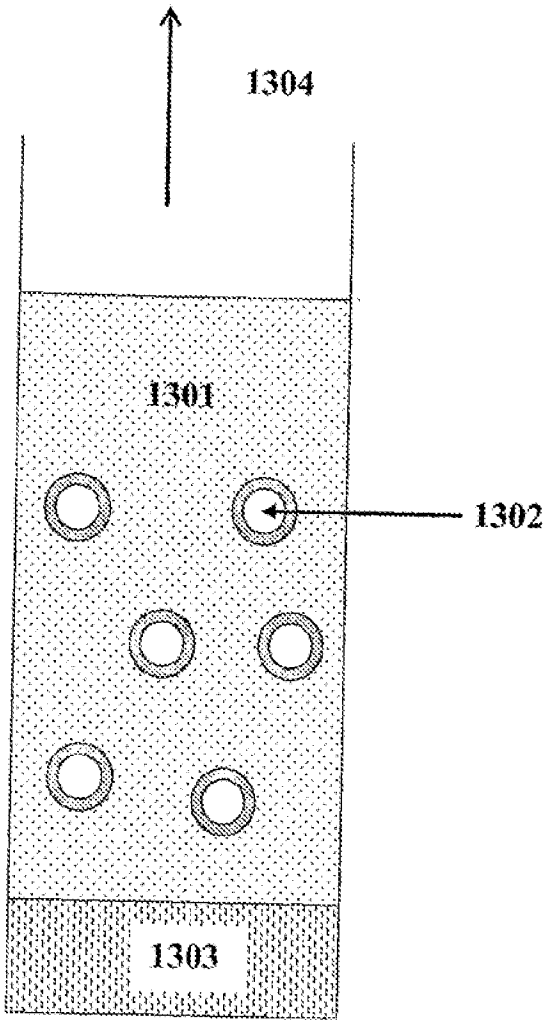


FIG. 14

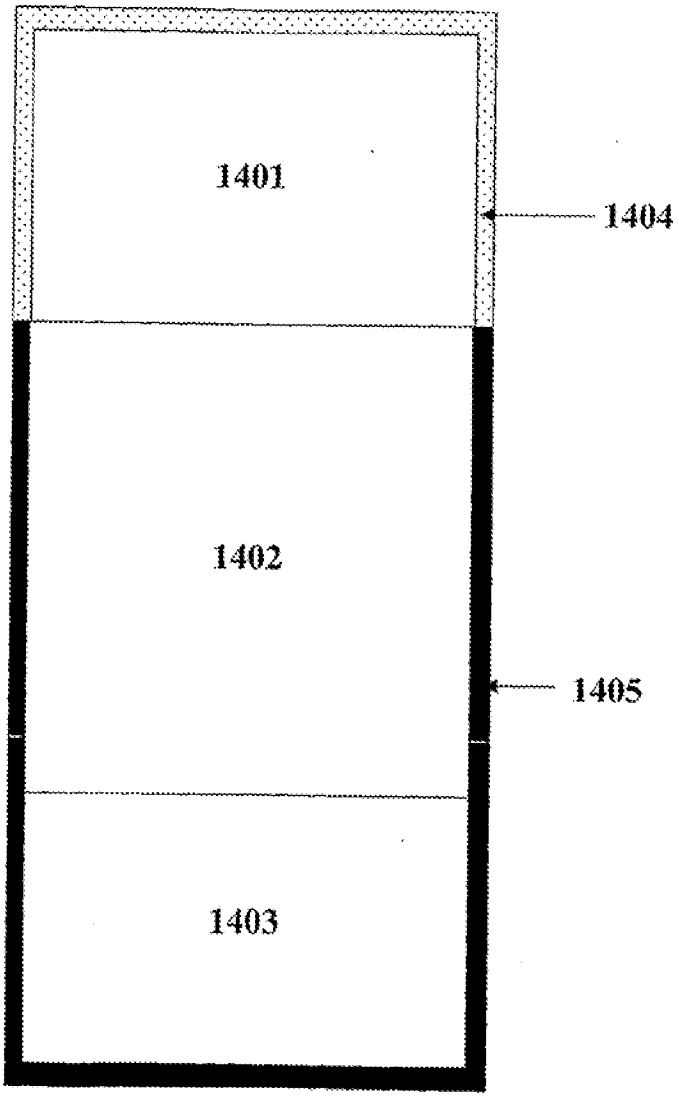


FIG. 15

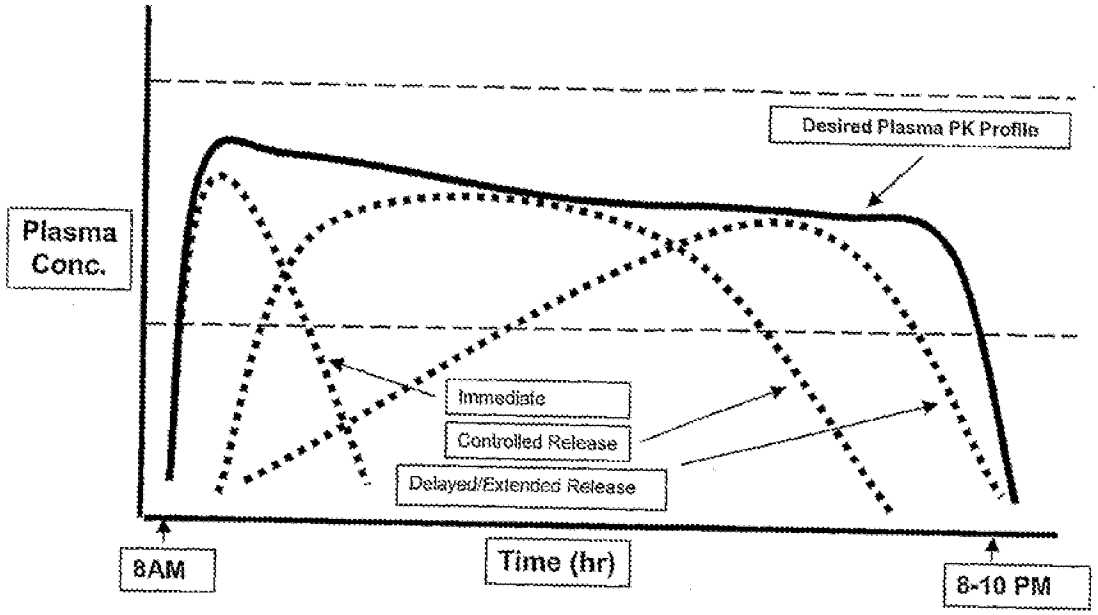

Desired Plasma PK Profile
Plasma Conc.
Immediate
Controlled Release
Delayed/Extended Release
8AM
Time (hr)
8-10 PM

FIG. 16

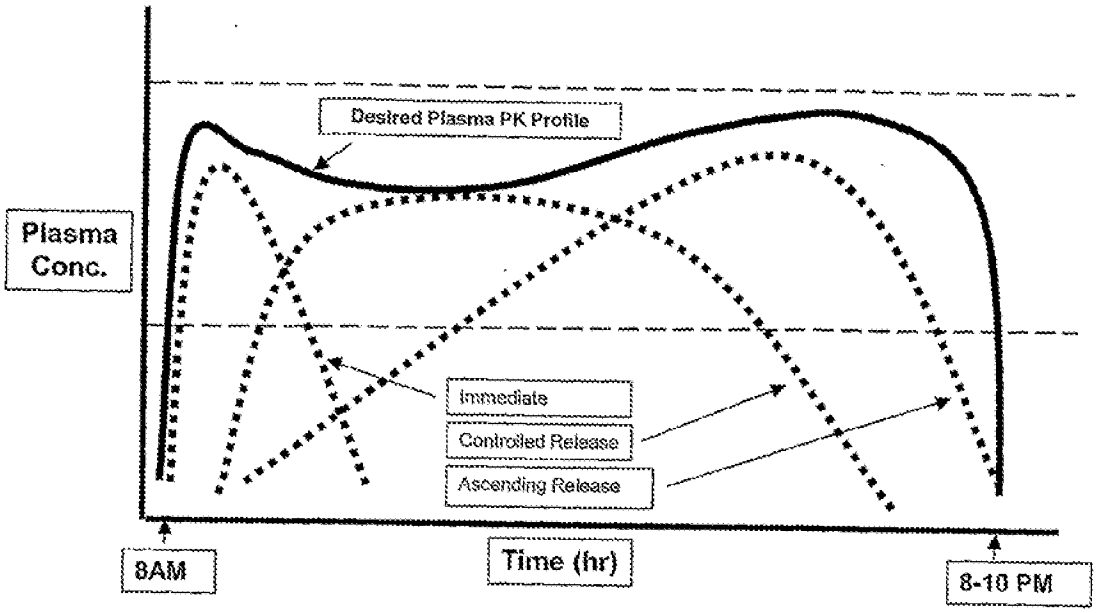

Desired Plasma PK Profile
Plasma Conc.
Immediate
Controlled Release
Ascending Release
8AM
Time (hr)
8-10 PM

FIG. 17

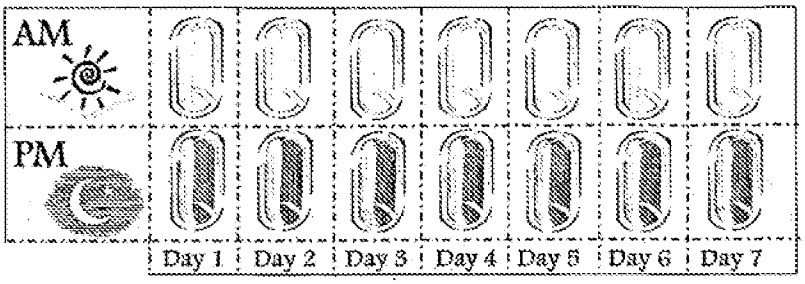


FIG. 18

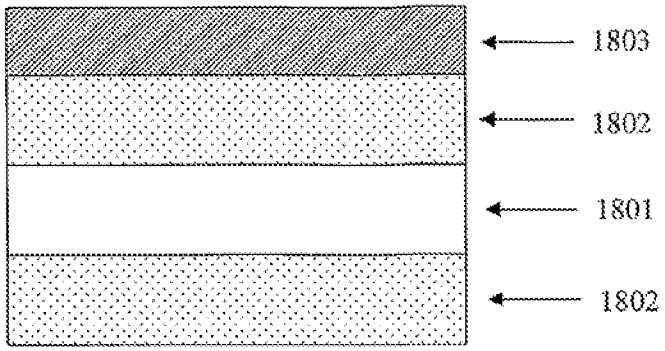


FIG. 19

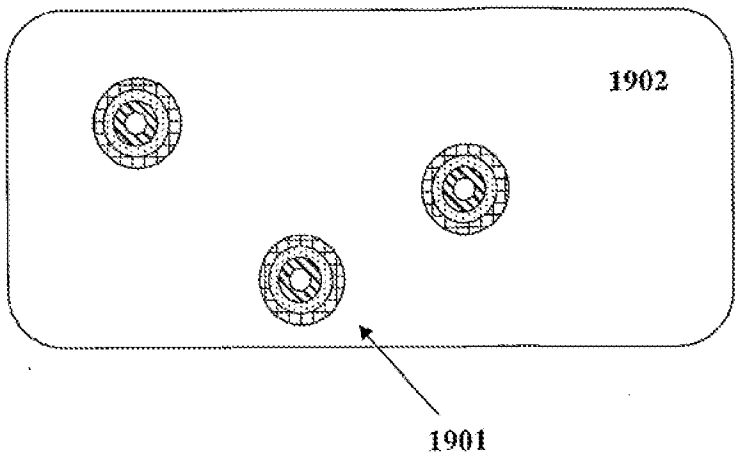


FIG. 20

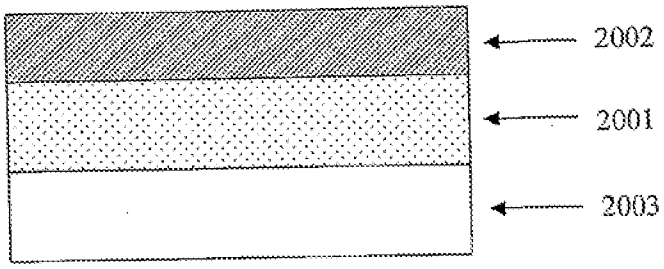


FIG. 21

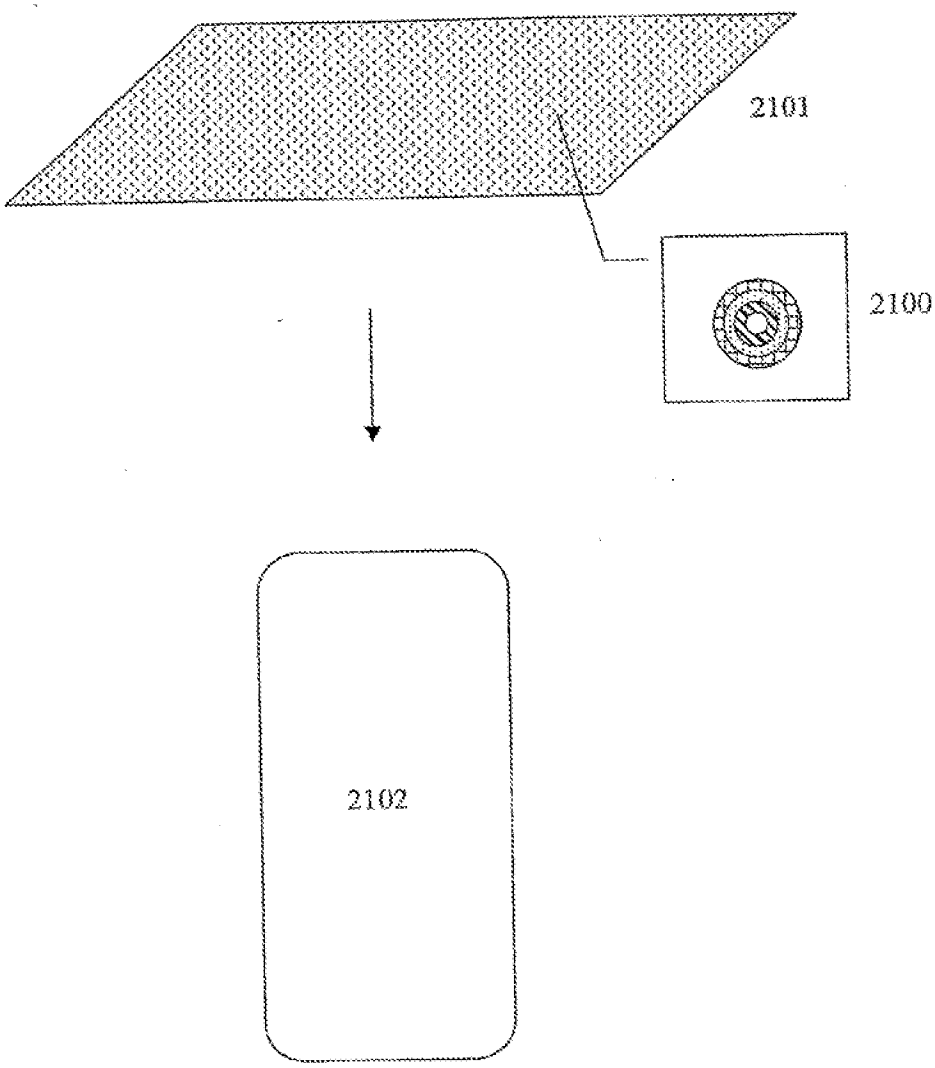
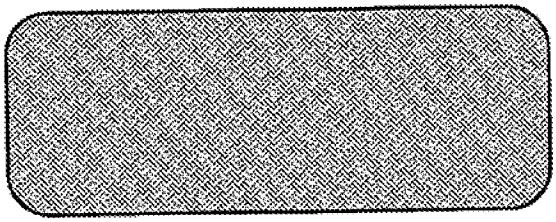
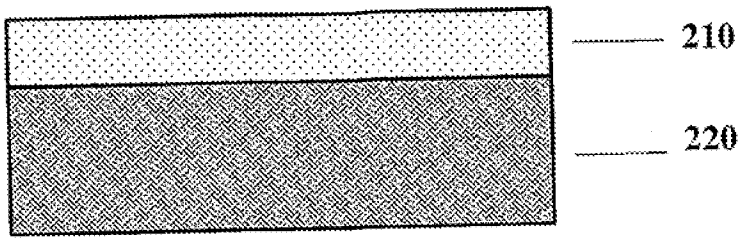


FIG. 22



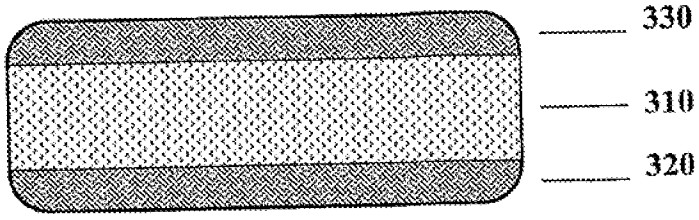
100

FIG. 23



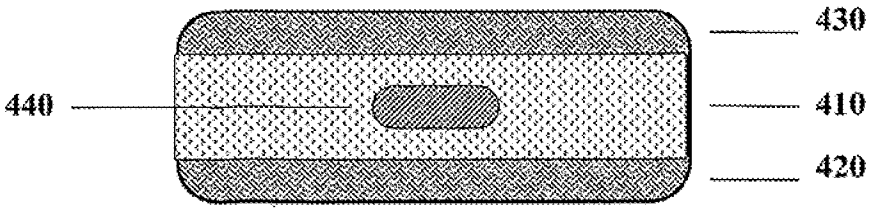
200

FIG. 24



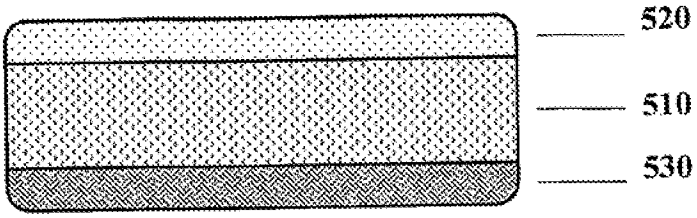
300

FIG. 25



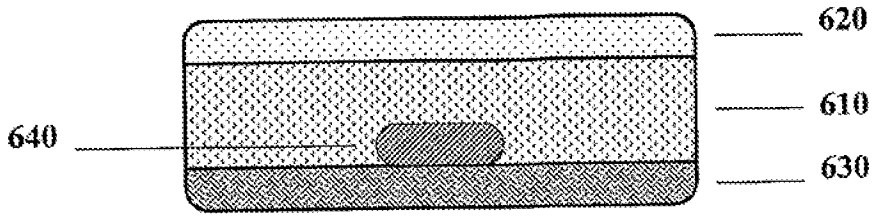
400

FIG. 26



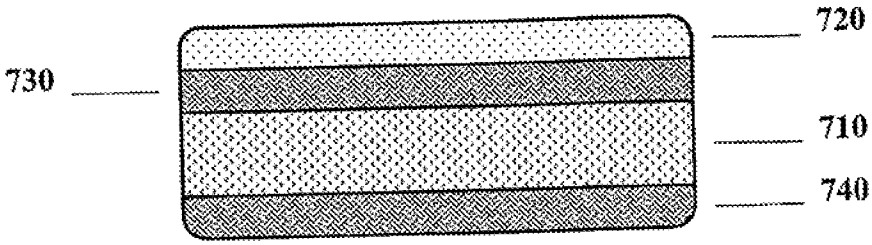
500

FIG. 27



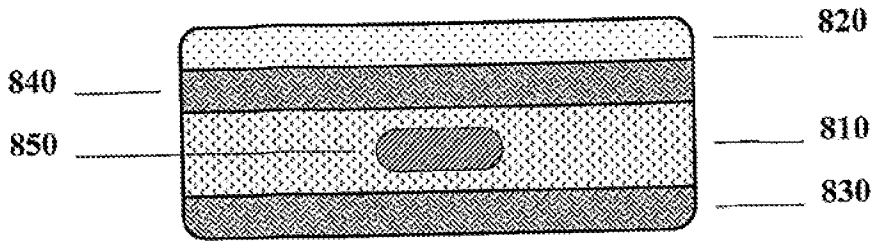
600

FIG. 28



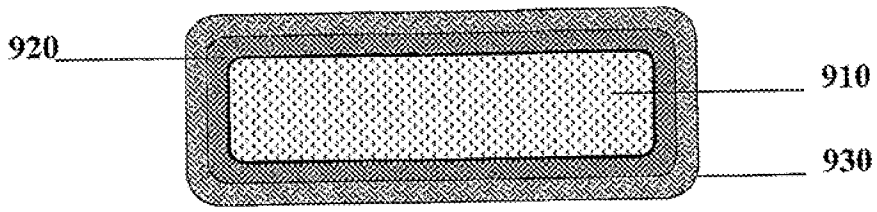
700

FIG. 29



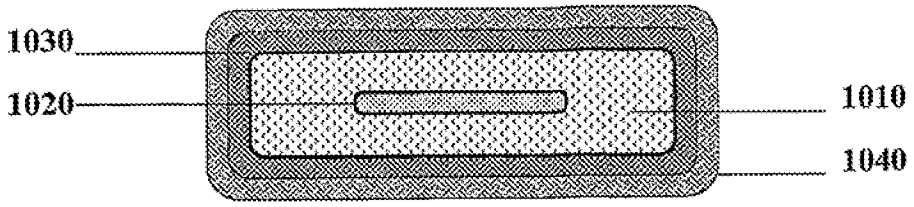
800

FIG. 30



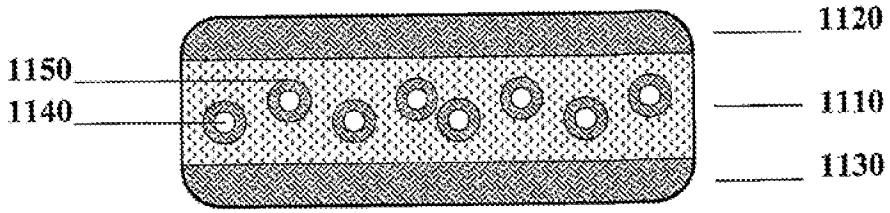
900

FIG. 31



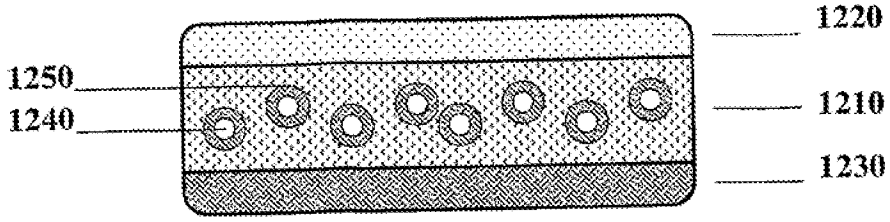
1000

FIG. 32



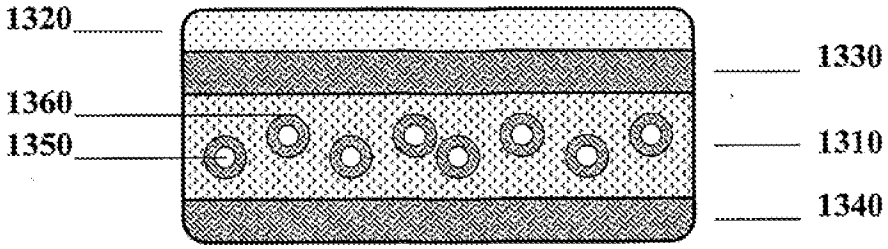
1100

FIG. 33



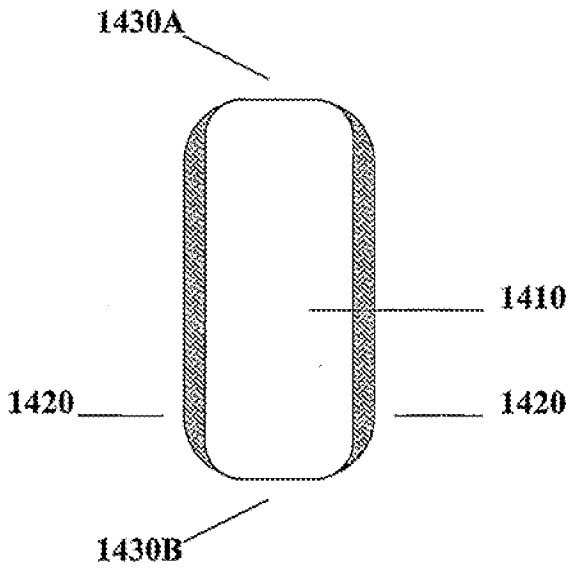
1200

FIG. 34



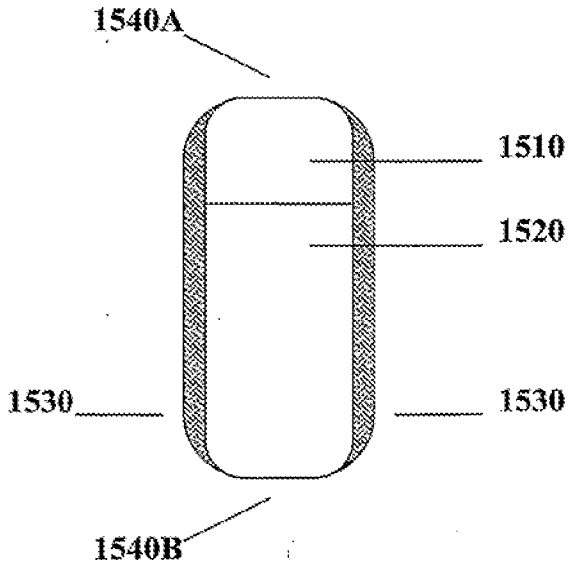
1300

FIG. 35



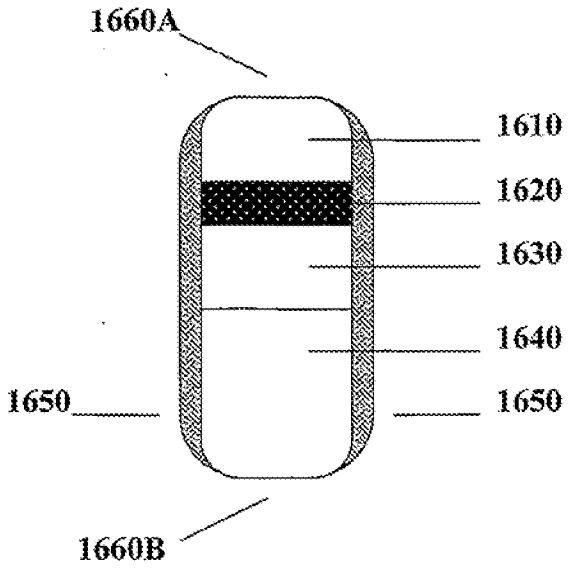
1400

FIG. 36



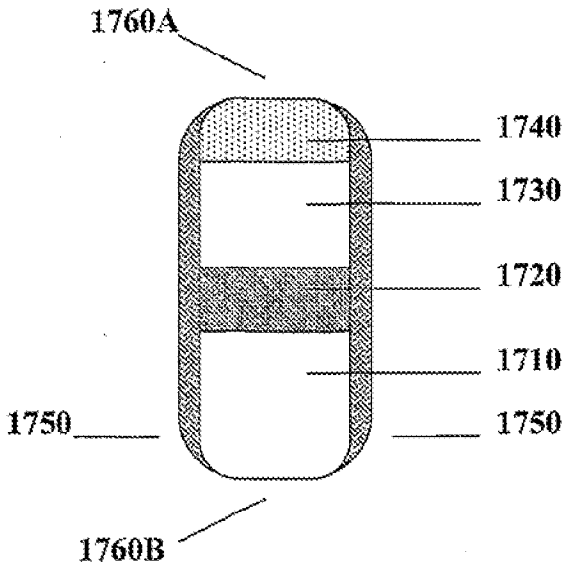
1500

FIG. 37



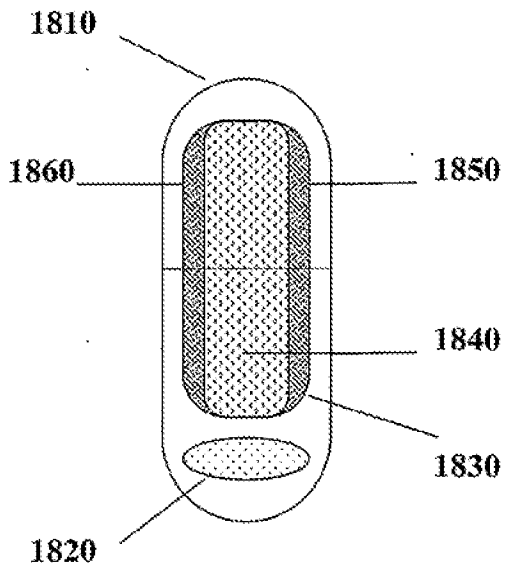
1600

FIG. 38



1700

FIG. 39



1800

FIG. 40

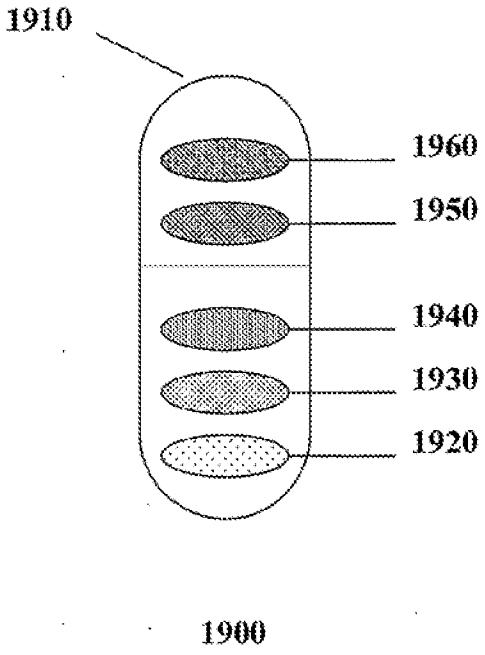
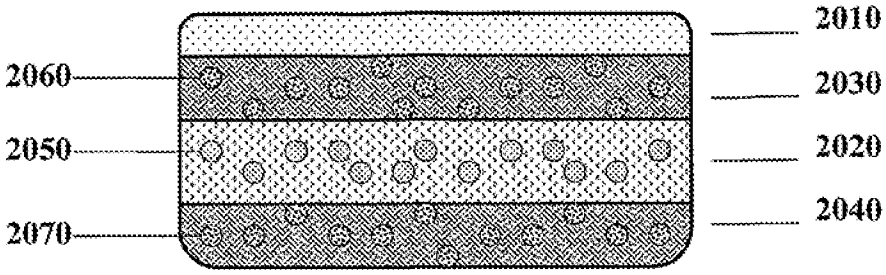
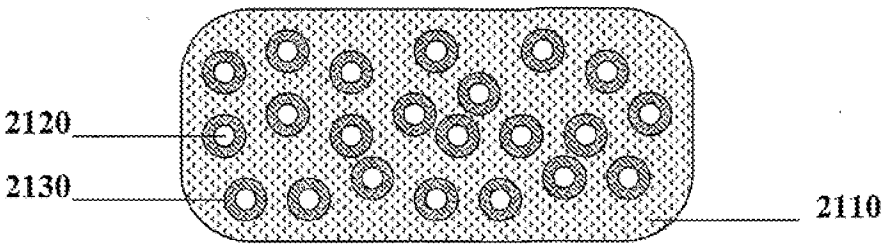


FIG. 41



2000

FIG. 42



2100

FIG. 43

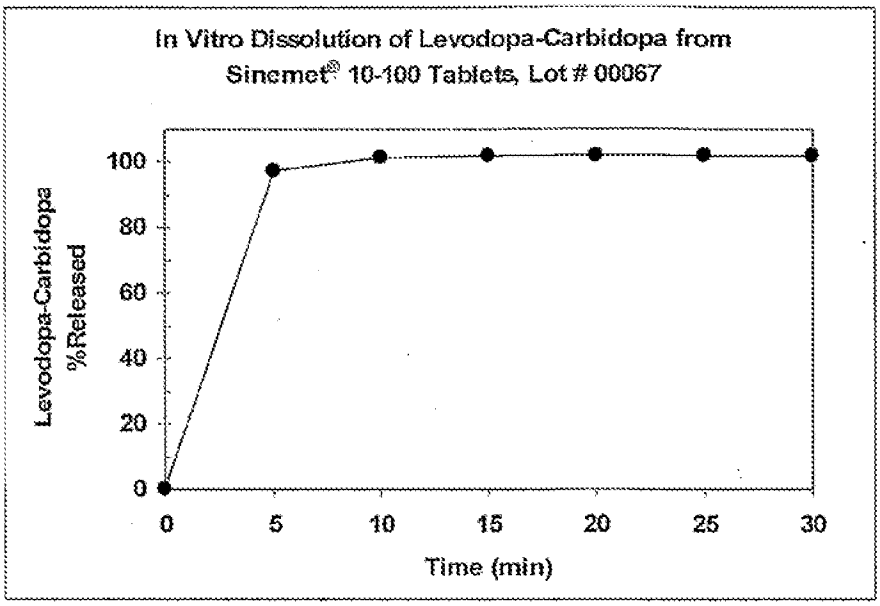

In Vitro Dissolution of Levodopa-Carbidopa from
Sinemet® 10-100 Tablets, Lot # 00067
Levodopa-Carbidopa
%Released
100
80
60
40
20
0
0
5
10
15
20
25
30
Time (min)

FIG. 44

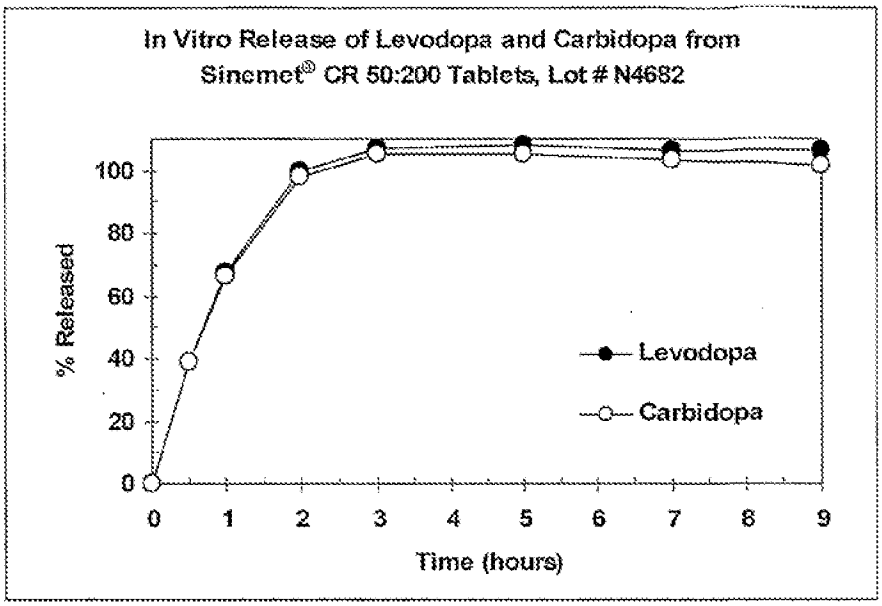

In Vitro Release of Levodopa and Carbidopa from
Sinemet® CR 50:200 Tablets, Lot # N4682
% Released
100
80
60
40
20
0
0
1
2
3
4
5
6
7
8
9
Time (hours)
Levodopa
Carbidopa

FIG. 45

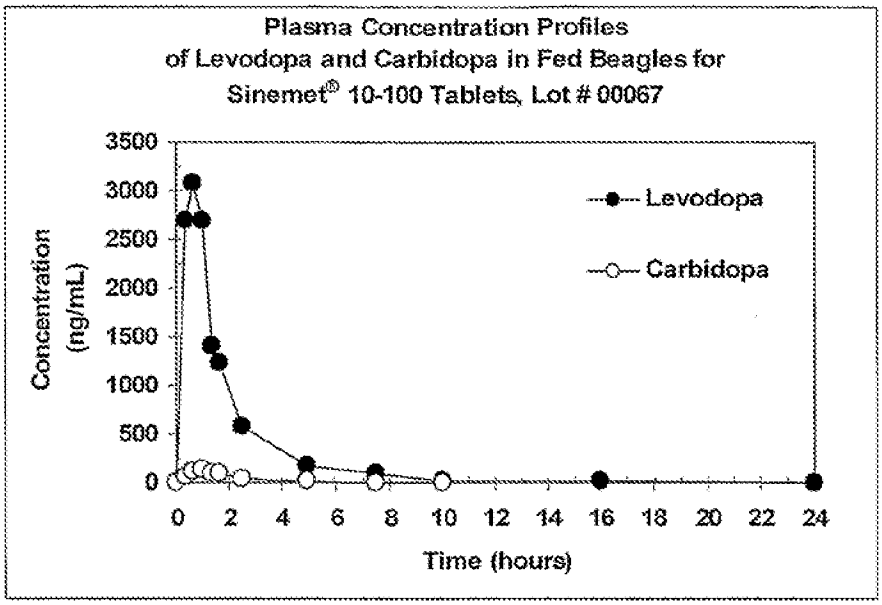

Plasma Concentration Profiles
of Levodopa and Carbidopa in Fed Beagles for
Sinemet® 10-100 Tablets, Lot # 00067
Concentration (ng/mL)
3500
3000
2500
2000
1500
1000
500
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)
Levodopa
Carbidopa

FIG. 46

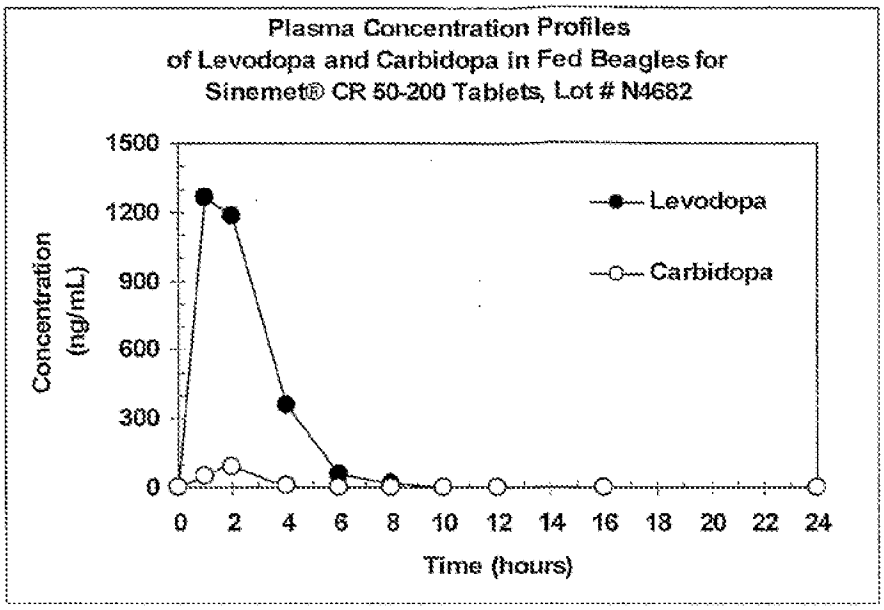

Plasma Concentration Profiles
of Levodopa and Carbidopa in Fed Beagles for
Sinemet® CR 50-200 Tablets, Lot # N4682
Concentration (ng/mL)
1500
1200
900
600
300
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)
Levodopa
Carbidopa

FIG. 47

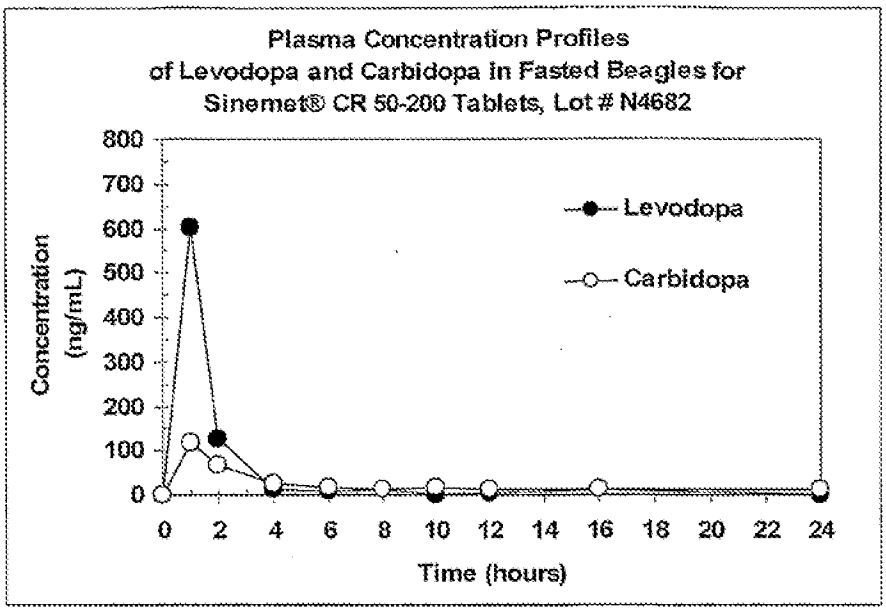

Plasma Concentration Profiles
of Levodopa and Carbidopa in Fasted Beagles for
Sinemet® CR 50-200 Tablets, Lot # N4682
Concentration (ng/mL)
800
700
600
500
400
300
200
100
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)
Levodopa
Carbidopa

FIG. 48

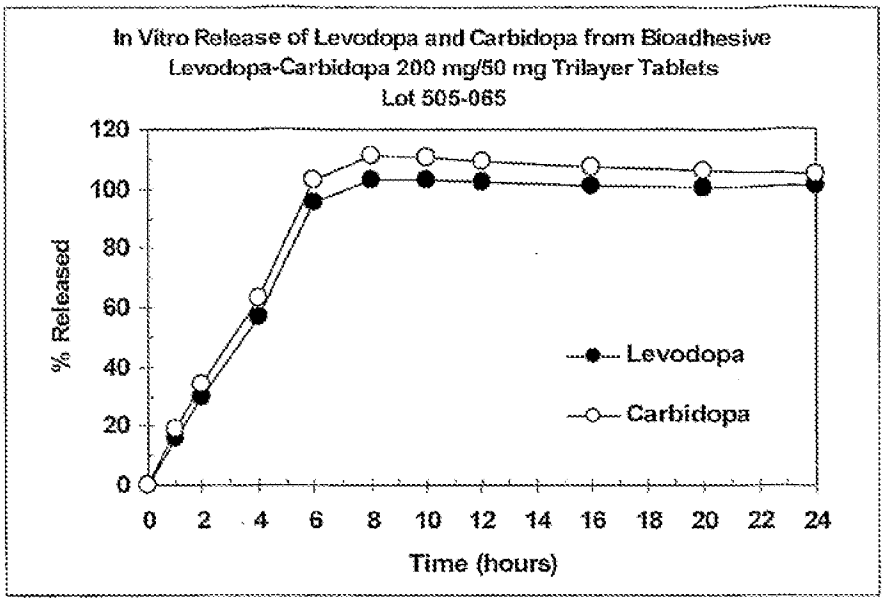

In Vitro Release of Levodopa and Carbidopa from Bioadhesive
Levodopa-Carbidopa 200 mg/50 mg Trilayer Tablets
Lot 505-065
% Released
120
100
80
60
40
20
0
0
2
4
6
8
10
12
14
16
18
20
22
24
Time (hours)
Levodopa
Carbidopa

FIG. 49

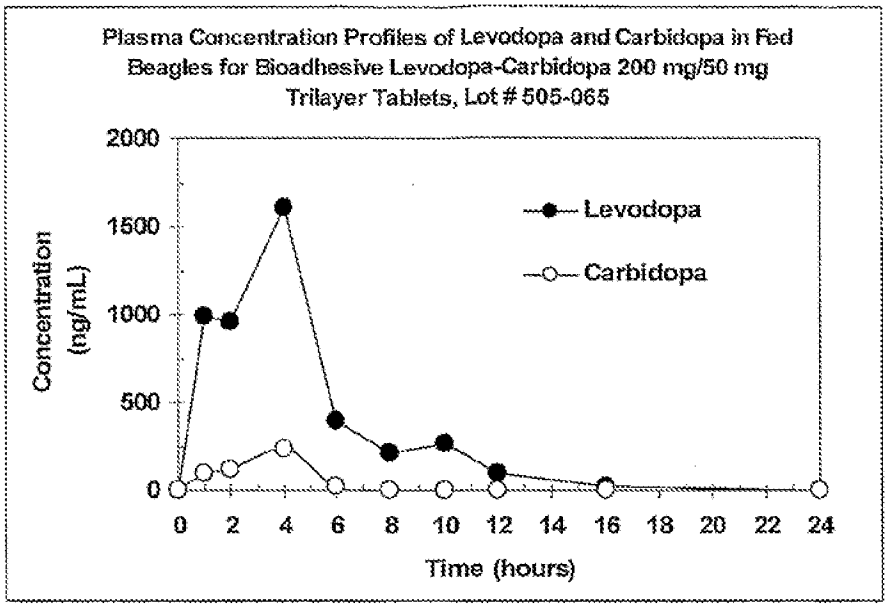

Plasma Concentration Profiles of Levodopa and Carbidopa in Fed Beagles for Bioadhesive Levodopa-Carbidopa 200 mg/50 mg Trilayer Tablets, Lot # 505-065
Concentration (ng/mL)
2000
1500
1000
500
0
Levodopa
Carbidopa
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)

FIG. 50

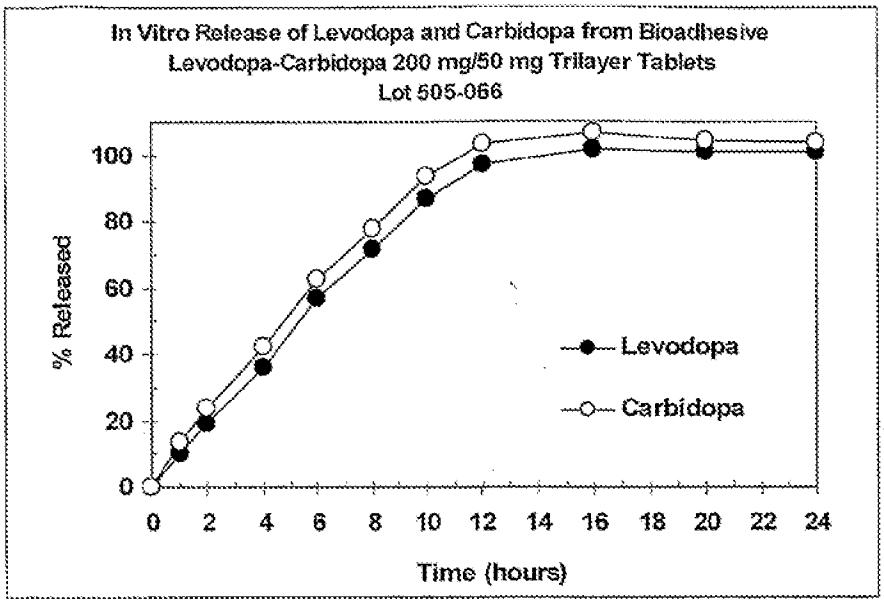

In Vitro Release of Levodopa and Carbidopa from Bioadhesive
Levodopa-Carbidopa 200 mg/50 mg Trilayer Tablets
Lot 505-066
% Released
100
80
60
40
20
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)
Levodopa
Carbidopa

FIG. 51

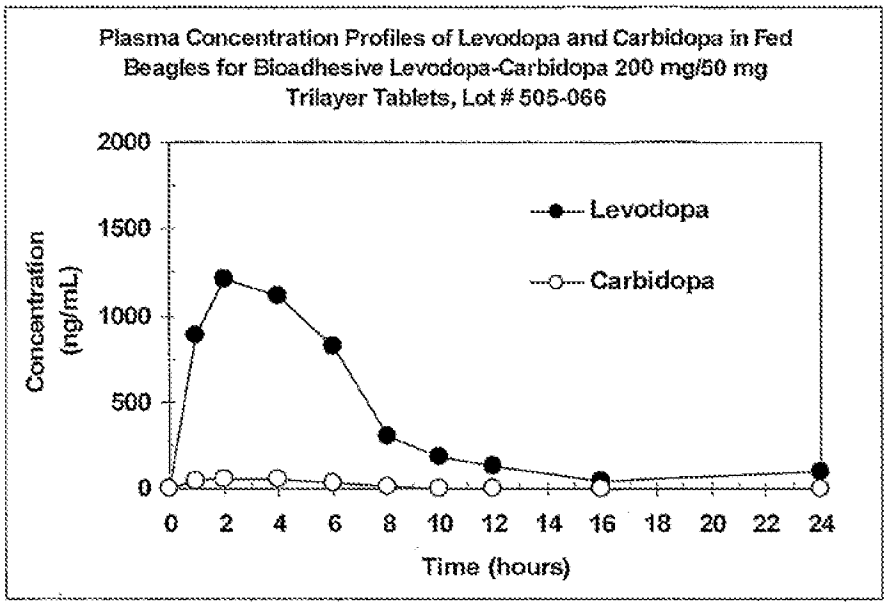

Plasma Concentration Profiles of Levodopa and Carbidopa in Fed Beagles for Bioadhesive Levodopa-Carbidopa 200 mg/50 mg Trilayer Tablets, Lot # 505-066
Concentration (ng/mL)
2000
1500
1000
500
0
Levodopa
Carbidopa
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)

FIG. 52

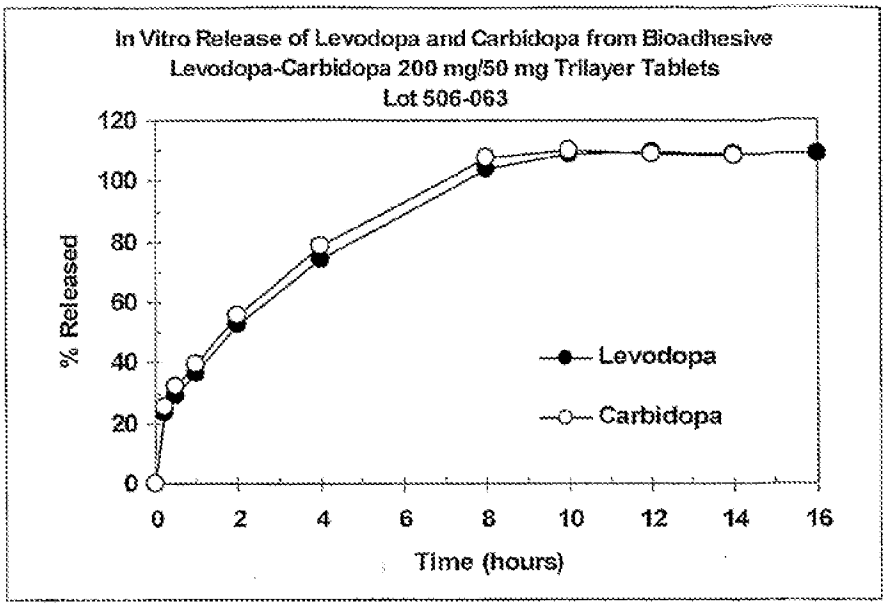

In Vitro Release of Levodopa and Carbidopa from Bioadhesive
Levodopa-Carbidopa 200 mg/50 mg Trilayer Tablets
Lot 506-063
% Released
120
100
80
60
40
20
0
0
2
4
6
8
10
12
14
16
Time (hours)
Levodopa
Carbidopa

FIG. 53

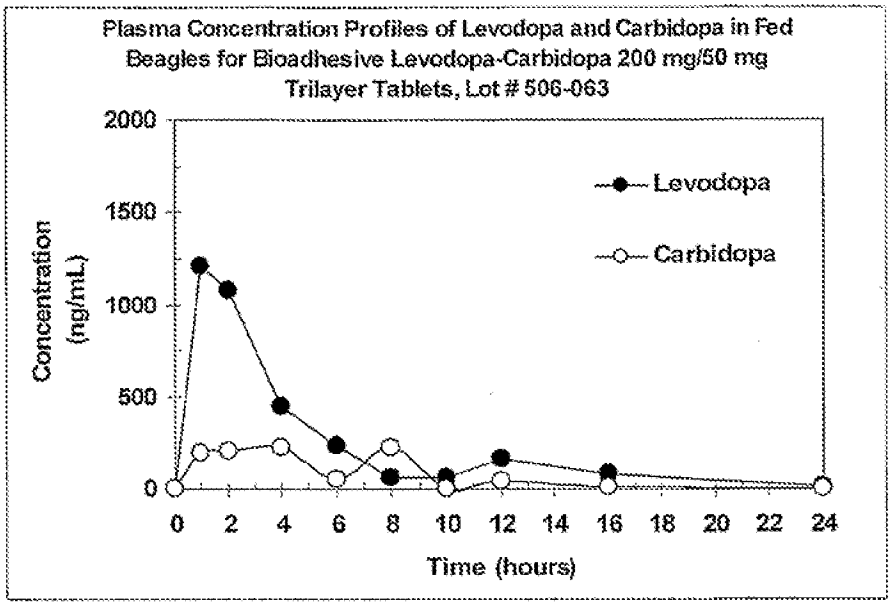

Plasma Concentration Profiles of Levodopa and Carbidopa in Fed Beagles for Bioadhesive Levodopa-Carbidopa 200 mg/50 mg Trilayer Tablets, Lot # 506-063
Concentration (ng/mL)
2000
1500
1000
500
0
Levodopa
Carbidopa
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)

FIG. 54

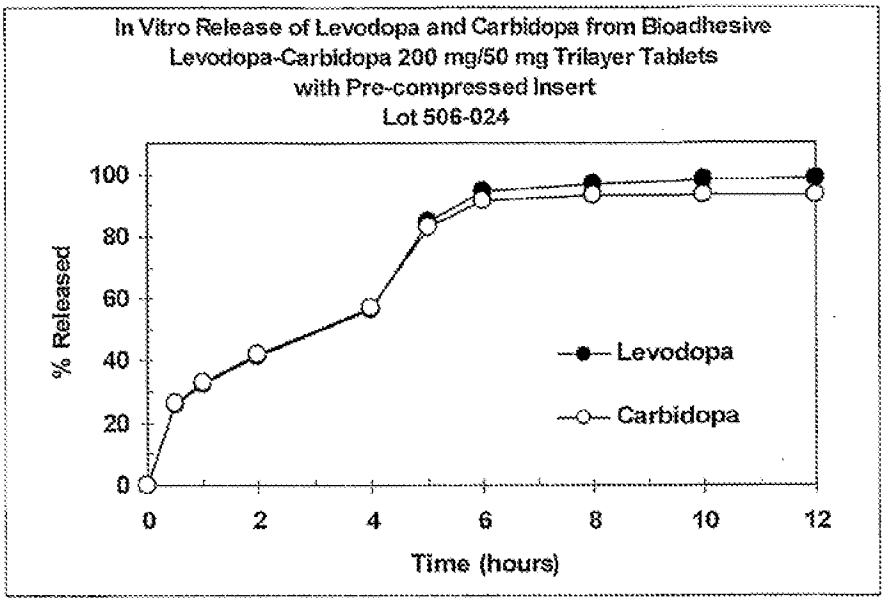

In Vitro Release of Levodopa and Carbidopa from Bioadhesive
Levodopa-Carbidopa 200 mg/50 mg Trilayer Tablets
with Pre-compressed Insert
Lot 506-024
% Released
100
80
60
40
20
0
0
2
4
6
8
10
12
Time (hours)
Levodopa
Carbidopa

FIG. 55

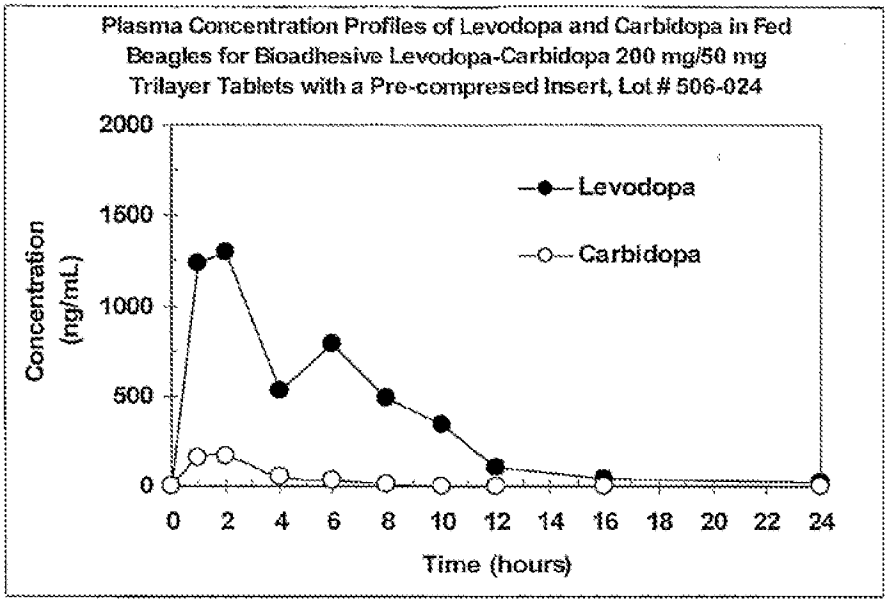

Plasma Concentration Profiles of Levodopa and Carbidopa in Fed Beagles for Bioadhesive Levodopa-Carbidopa 200 mg/50 mg Trilayer Tablets with a Pre-compresed Insert, Lot # 506-024
Concentration (ng/mL)
2000
1500
1000
500
0
Levodopa
Carbidopa
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)

FIG. 56

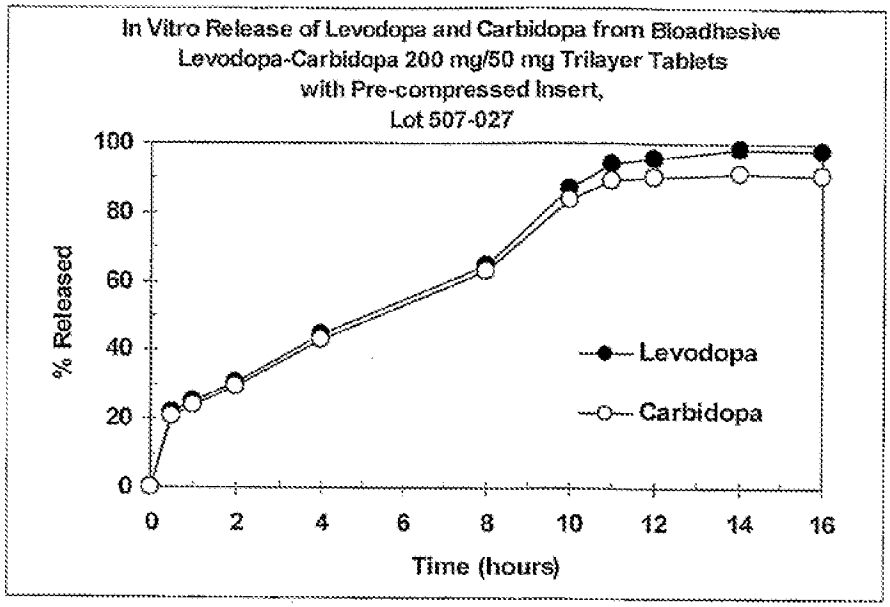

In Vitro Release of Levodopa and Carbidopa from Bioadhesive
Levodopa-Carbidopa 200 mg/50 mg Trilayer Tablets
with Pre-compressed Insert,
Lot 507-027
% Released
100
80
60
40
20
0
0
2
4
6
8
10
12
14
16
Time (hours)
Levodopa
Carbidopa

FIG. 57

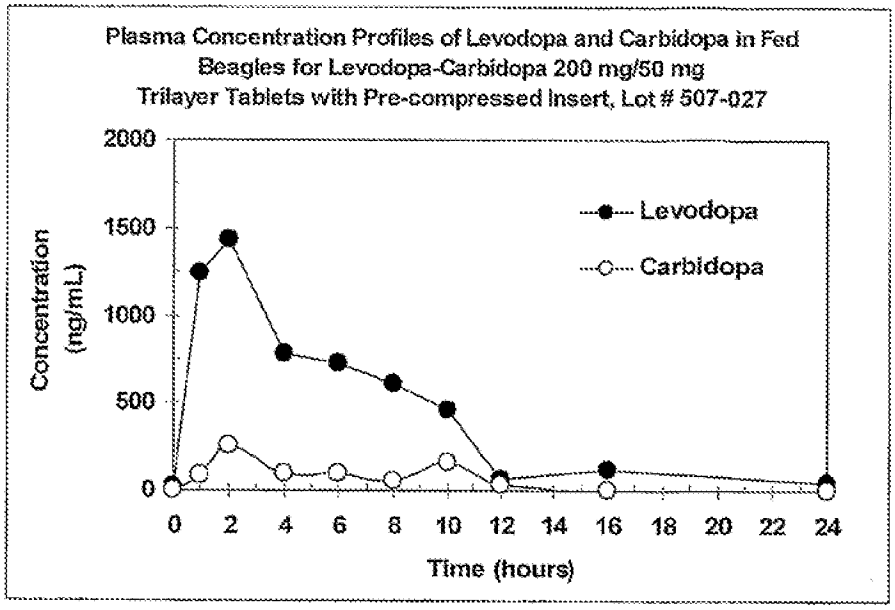

Plasma Concentration Profiles of Levodopa and Carbidopa in Fed Beagles for Levodopa-Carbidopa 200 mg/50 mg Trilayer Tablets with Pre-compressed Insert, Lot # 507-027
Concentration (ng/mL)
2000
1500
1000
500
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)
Levodopa
Carbidopa

FIG. 58

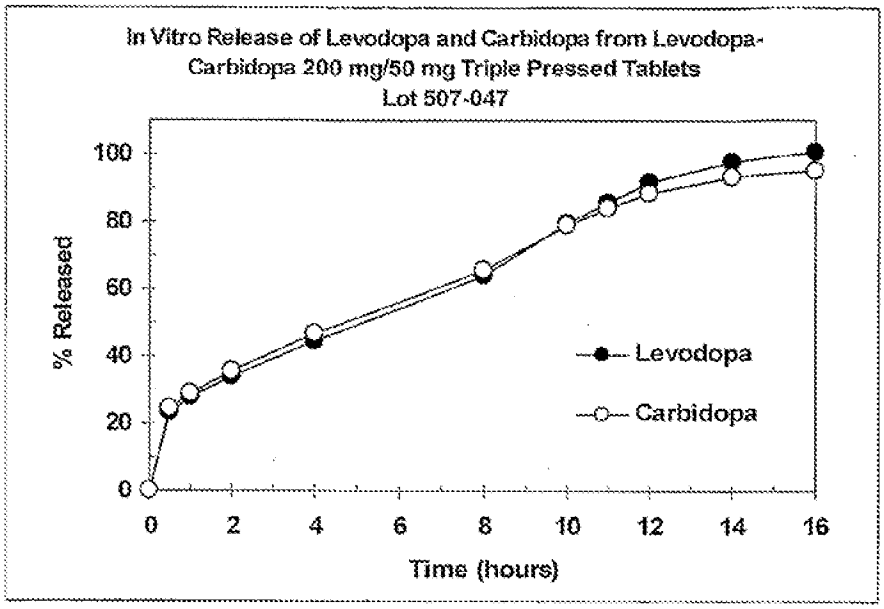

In Vitro Release of Levodopa and Carbidopa from Levodopa-Carbidopa 200 mg/50 mg Triple Pressed Tablets
Lot 507-047
% Released
100
80
60
40
20
0
0
2
4
6
8
10
12
14
16
Time (hours)
Levodopa
Carbidopa

FIG. 59

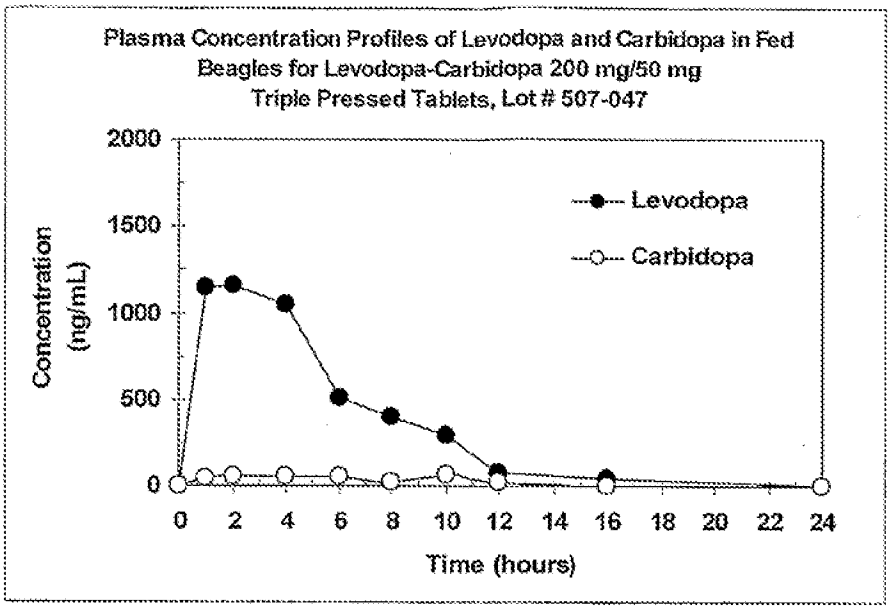

Plasma Concentration Profiles of Levodopa and Carbidopa in Fed Beagles for Levodopa-Carbidopa 200 mg/50 mg Triple Pressed Tablets, Lot # 507-047
Concentration (ng/mL)
2000
1500
1000
500
0
Levodopa
Carbidopa
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)

FIG. 60

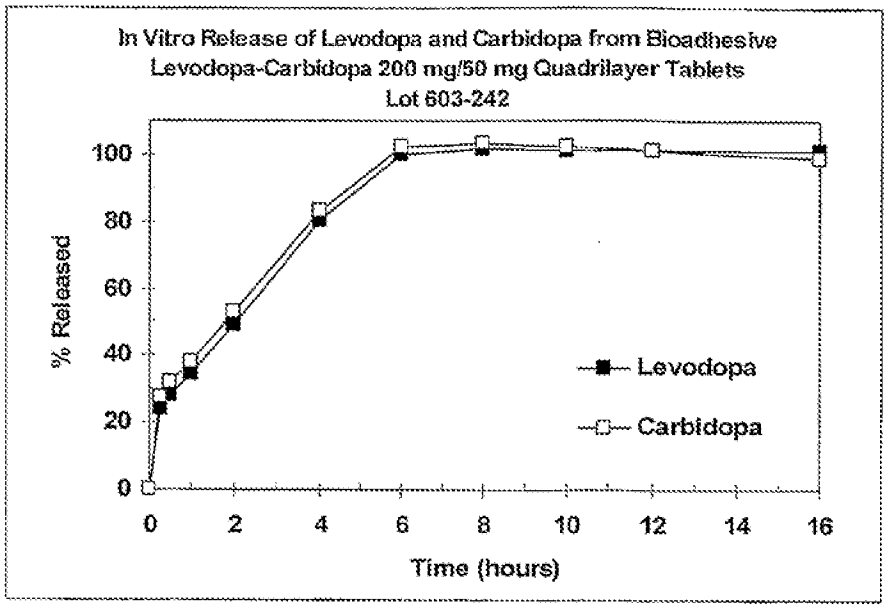

In Vitro Release of Levodopa and Carbidopa from Bioadhesive
Levodopa-Carbidopa 200 mg/50 mg Quadrilayer Tablets
Lot 603-242
% Released
100
80
60
40
20
0
0
2
4
6
8
10
12
14
16
Time (hours)
Levodopa
Carbidopa

FIG. 61

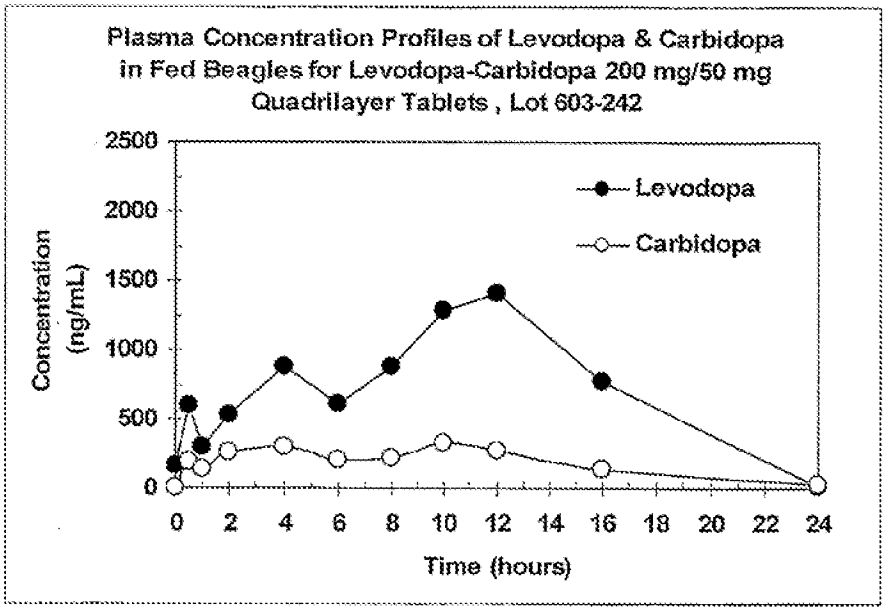

Plasma Concentration Profiles of Levodopa & Carbidopa
in Fed Beagles for Levodopa-Carbidopa 200 mg/50 mg
Quadrilayer Tablets , Lot 603-242
Concentration (ng/mL)
2500
2000
1500
1000
500
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)
Levodopa
Carbidopa

FIG. 62

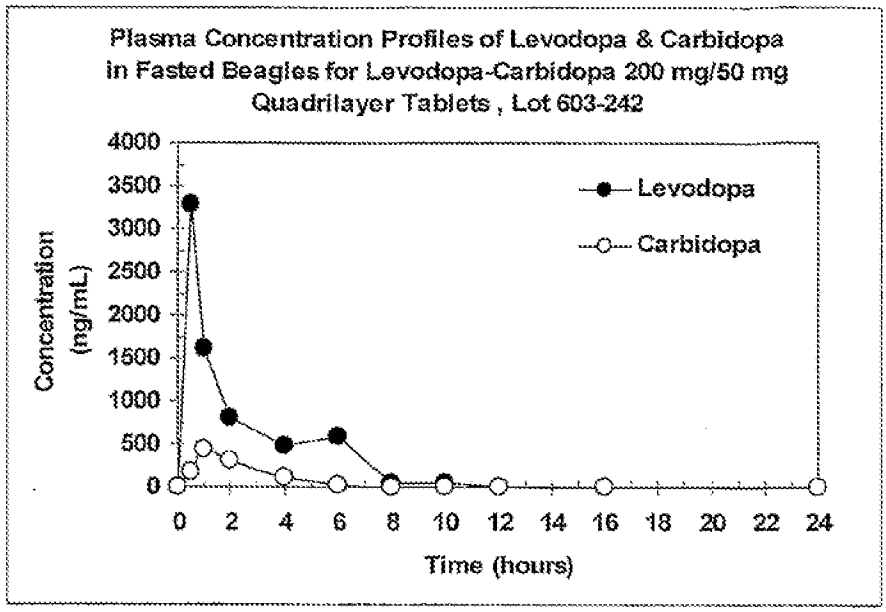

Plasma Concentration Profiles of Levodopa & Carbidopa
in Fasted Beagles for Levodopa-Carbidopa 200 mg/50 mg
Quadrilayer Tablets , Lot 603-242
Concentration (ng/mL)
4000
3500
3000
2500
2000
1500
1000
500
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)
Levodopa
Carbidopa

FIG. 63

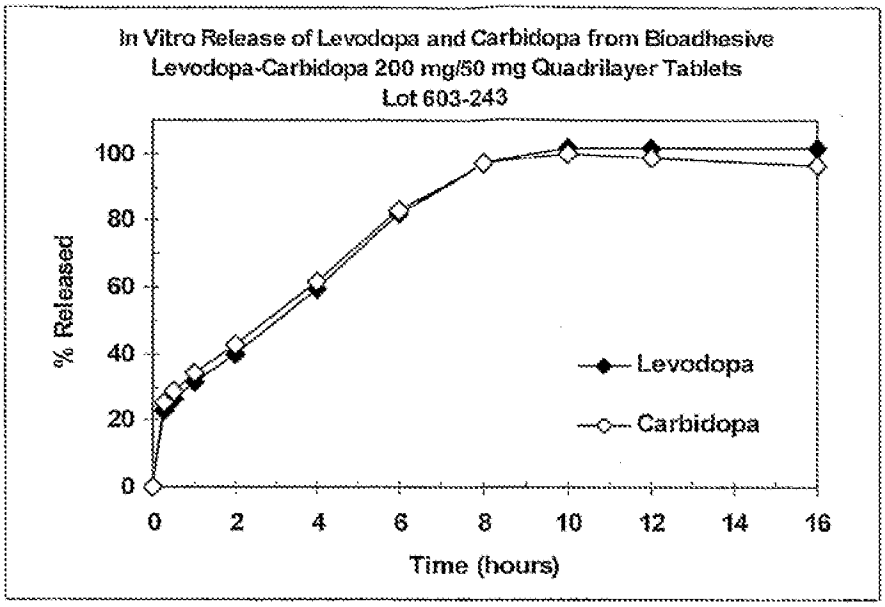

In Vitro Release of Levodopa and Carbidopa from Bioadhesive
Levodopa-Carbidopa 200 mg/50 mg Quadrilayer Tablets
Lot 603-243
% Released
100
80
60
40
20
0
0
2
4
6
8
10
12
14
16
Time (hours)
Levodopa
Carbidopa

FIG. 64

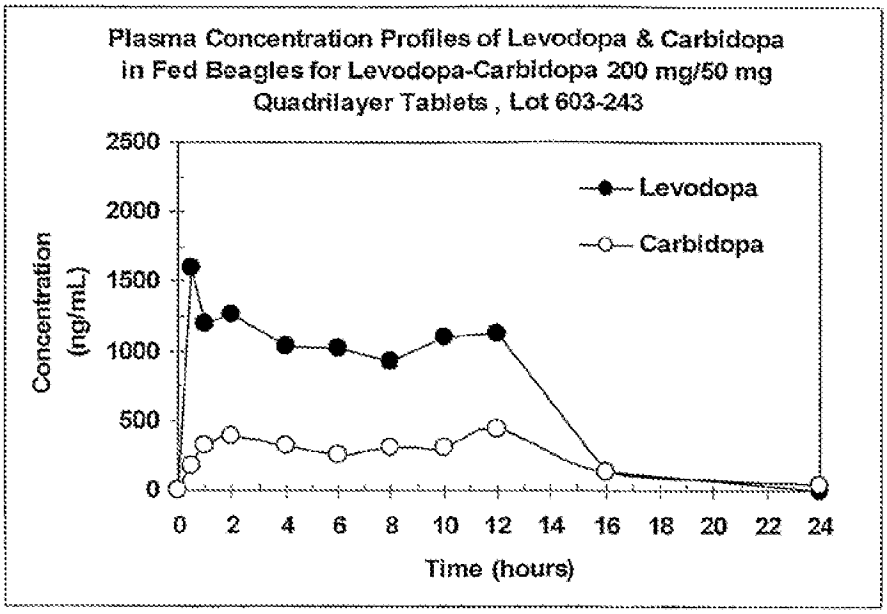

Plasma Concentration Profiles of Levodopa & Carbidopa
in Fed Beagles for Levodopa-Carbidopa 200 mg/50 mg
Quadrilayer Tablets , Lot 603-243
Concentration (ng/mL)
2500
2000
1500
1000
500
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)
Levodopa
Carbidopa

FIG. 65

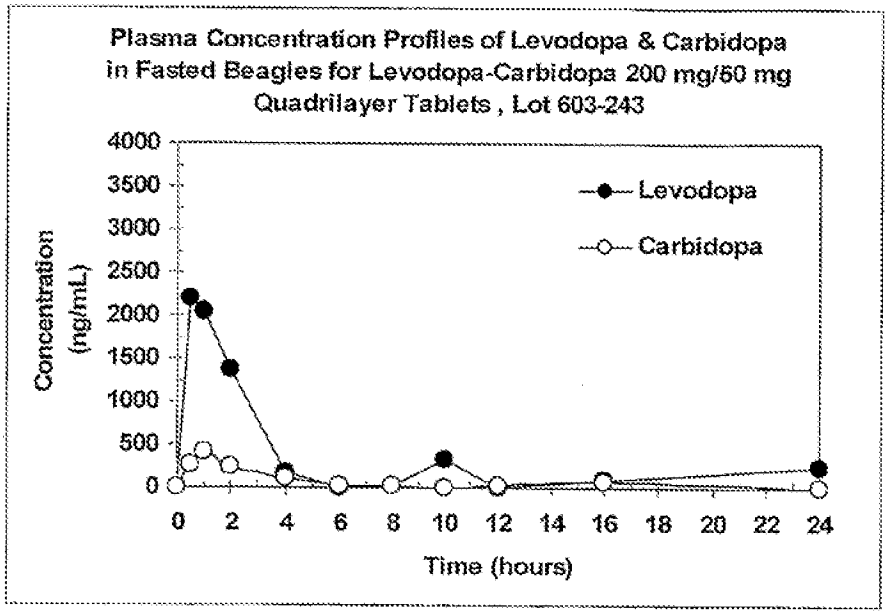

Plasma Concentration Profiles of Levodopa & Carbidopa
in Fasted Beagles for Levodopa-Carbidopa 200 mg/50 mg
Quadrilayer Tablets , Lot 603-243
Concentration (ng/mL)
4000
3500
3000
2500
2000
1500
1000
500
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)
Levodopa
Carbidopa

FIG. 66

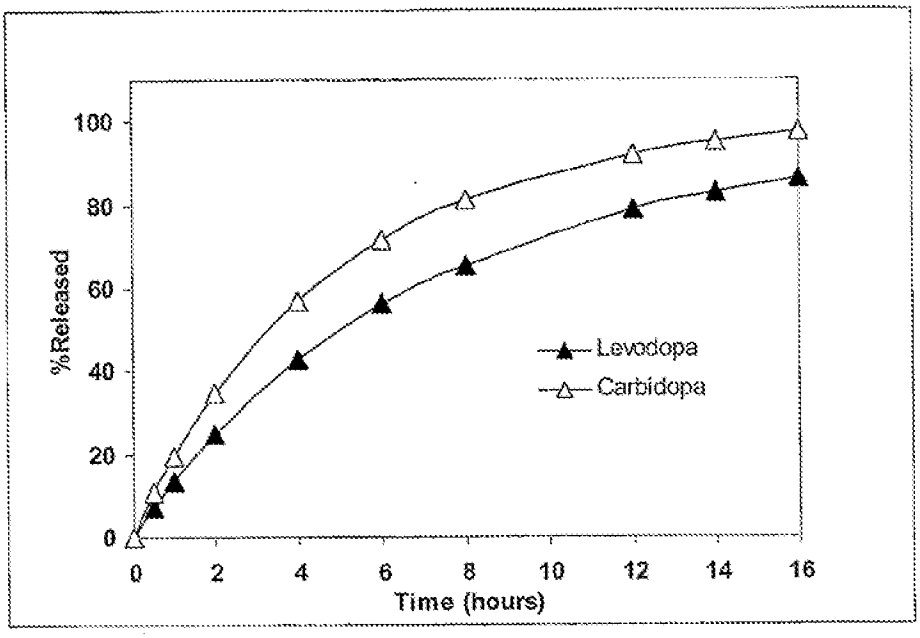

100
80
60
40
20
0
% Released
0
2
4
6
8
10
12
14
16
Time (hours)
Levodopa
Carbidopa

FIG. 67

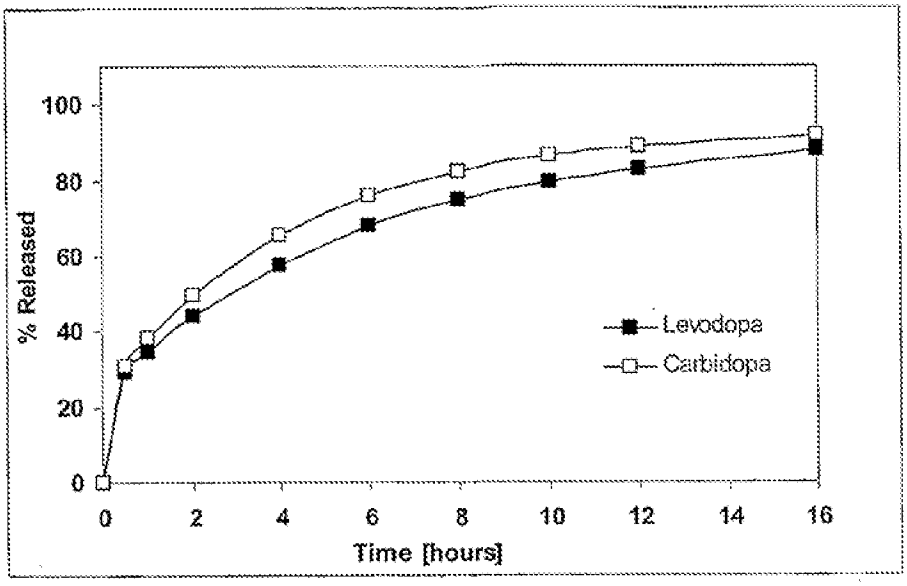

100
80
60
40
20
0
% Released
0
2
4
6
8
10
12
14
16
Time [hours]
Levodopa
Carbidopa

FIG. 68

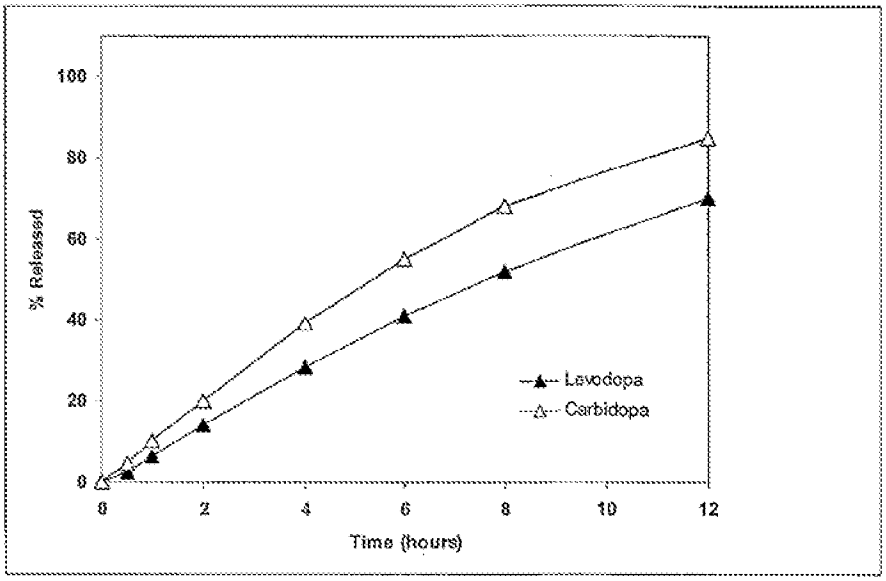

100
80
60
40
20
0
% Released
0
2
4
6
8
10
12
Time (hours)
Levodopa
Carbidopa

FIG. 69

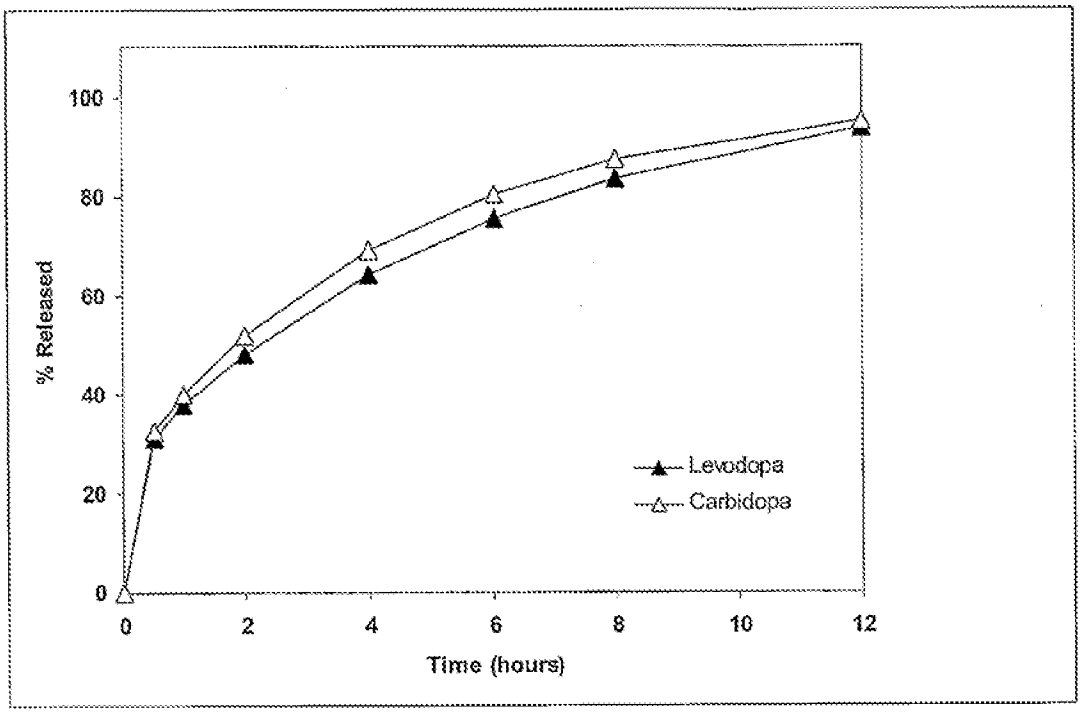

100
80
60
40
20
0
% Released
0
2
4
6
8
10
12
Time (hours)
Levodopa
Carbidopa

FIG. 70

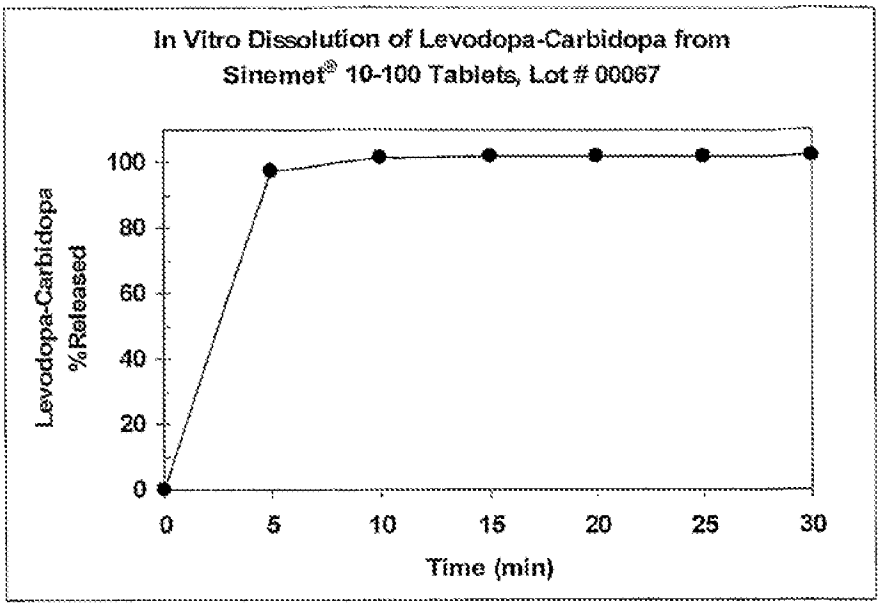

In Vitro Dissolution of Levodopa-Carbidopa from
Sinemet® 10-100 Tablets, Lot # 00067
Levodopa-Carbidopa
%Released
100
80
60
40
20
0
0
5
10
15
20
25
30
Time (min)

FIG. 71

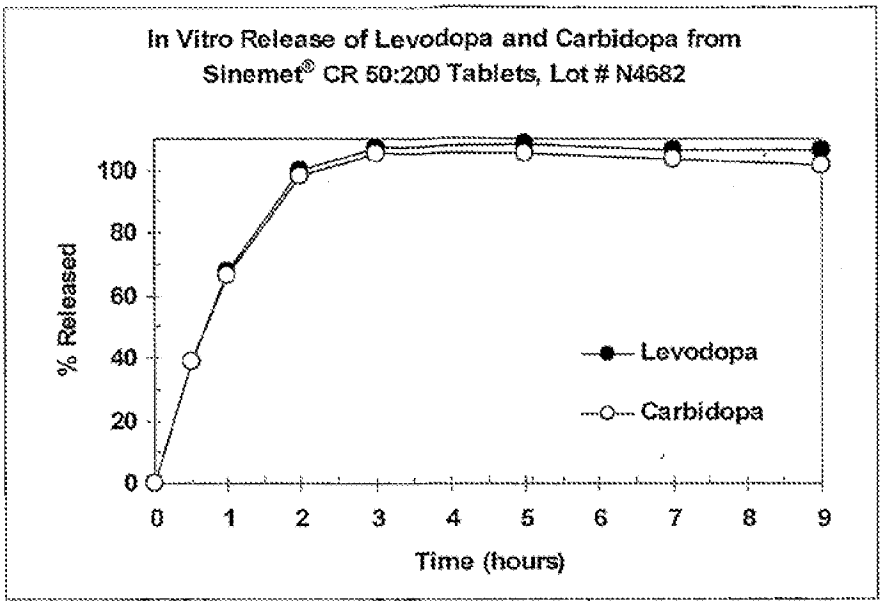

In Vitro Release of Levodopa and Carbidopa from
Sinemet® CR 50:200 Tablets, Lot # N4682
% Released
100
80
60
40
20
0
0
1
2
3
4
5
6
7
8
9
Time (hours)
Levodopa
Carbidopa

FIG. 72

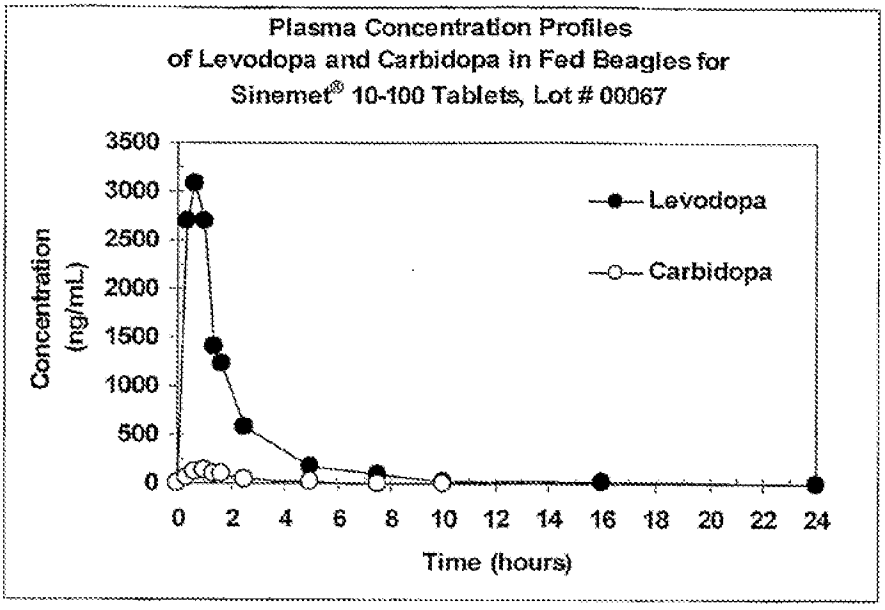

Plasma Concentration Profiles
of Levodopa and Carbidopa in Fed Beagles for
Sinemet® 10-100 Tablets, Lot # 00067
Concentration (ng/mL)
3500
3000
2500
2000
1500
1000
500
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)
Levodopa
Carbidopa

FIG. 73

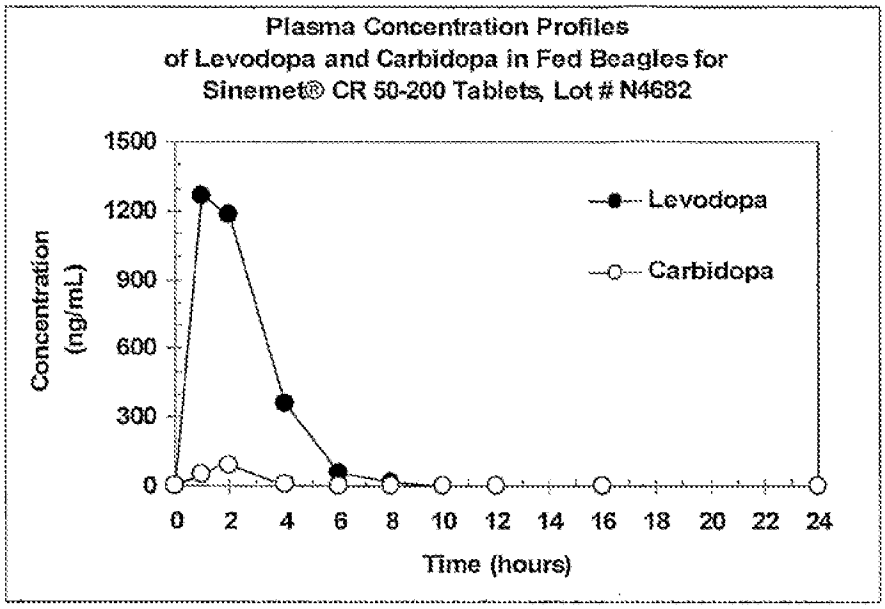

Plasma Concentration Profiles
of Levodopa and Carbidopa in Fed Beagles for
Sinemet® CR 50-200 Tablets, Lot # N4682
Concentration (ng/mL)
1500
1200
900
600
300
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)
Levodopa
Carbidopa

FIG. 74

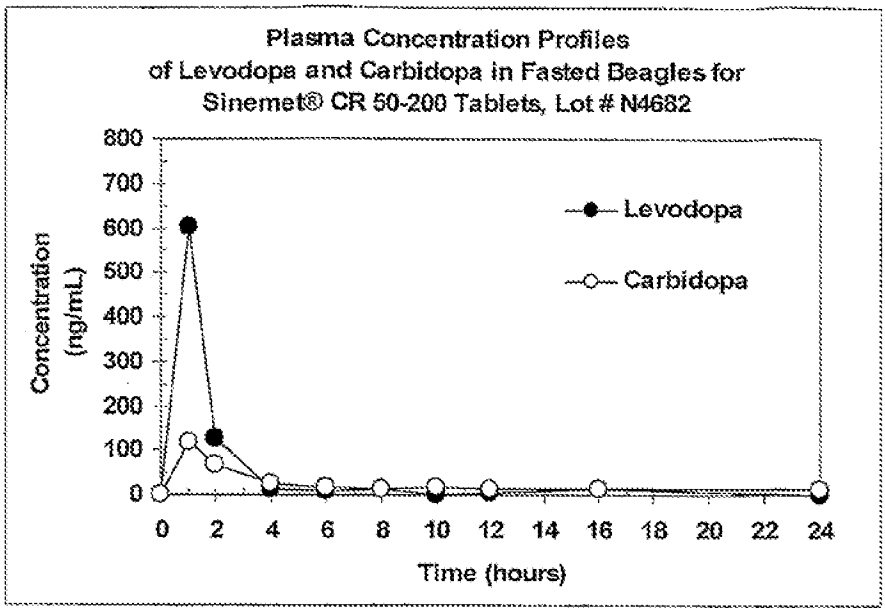

Plasma Concentration Profiles
of Levodopa and Carbidopa in Fasted Beagles for
Sinemet® CR 50-200 Tablets, Lot # N4682
Concentration (ng/mL)
800
700
600
500
400
300
200
100
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)
Levodopa
Carbidopa

FIG. 75

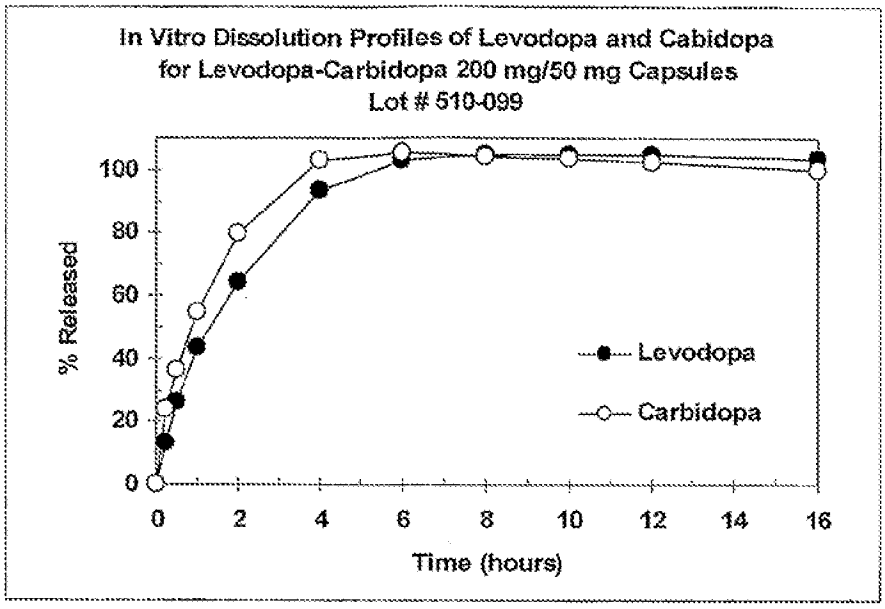

In Vitro Dissolution Profiles of Levodopa and Cabidopa
for Levodopa-Carbidopa 200 mg/50 mg Capsules
Lot # 510-099
% Released
100
80
60
40
20
0
0
2
4
6
8
10
12
14
16
Time (hours)
Levodopa
Carbidopa

FIG. 76

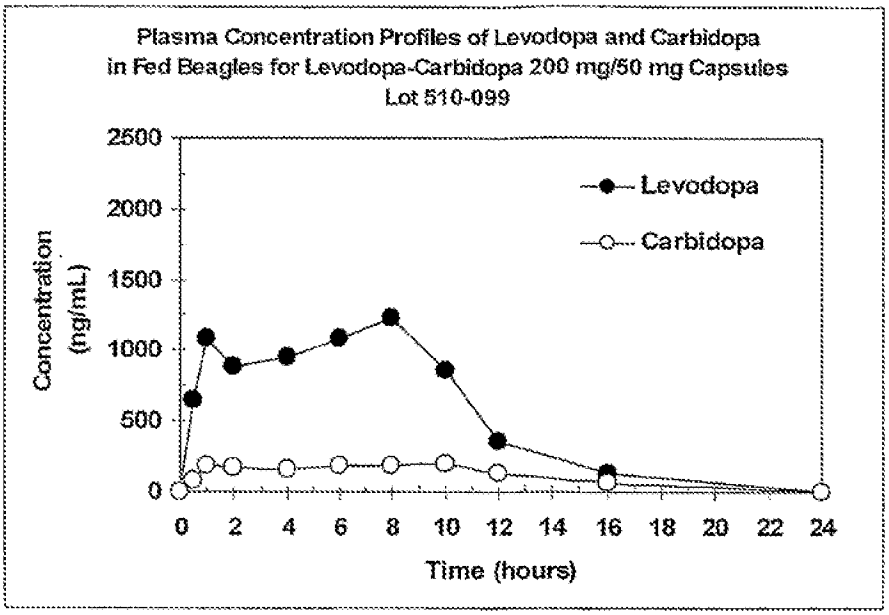

Plasma Concentration Profiles of Levodopa and Carbidopa
in Fed Beagles for Levodopa-Carbidopa 200 mg/50 mg Capsules
Lot 510-099
Concentration (ng/mL)
2500
2000
1500
1000
500
0
Levodopa
Carbidopa
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)

FIG. 77

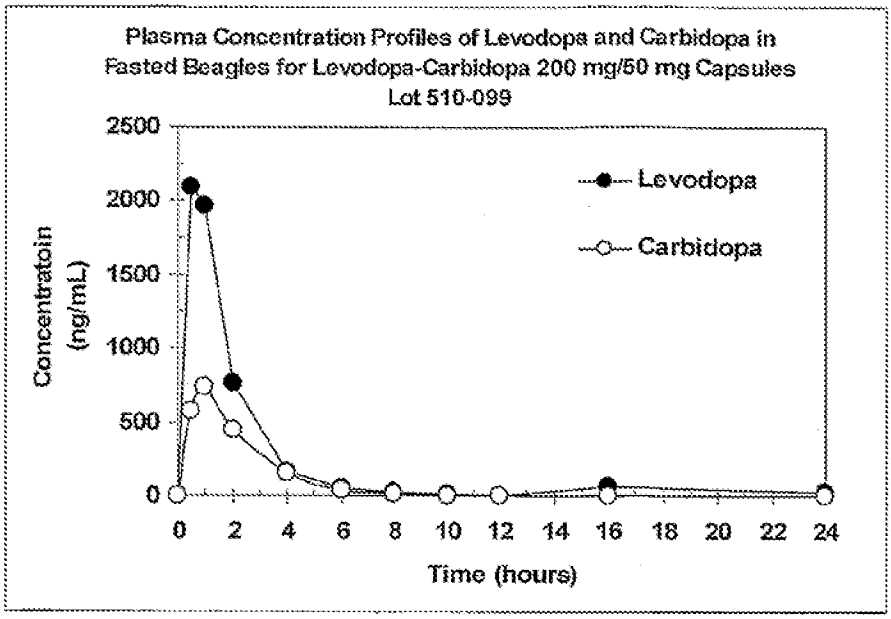

Plasma Concentration Profiles of Levodopa and Carbidopa in Fasted Beagles for Levodopa-Carbidopa 200 mg/50 mg Capsules Lot 510-099
Concentratoin (ng/mL)
2500
2000
1500
1000
500
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)
Levodopa
Carbidopa

FIG. 78

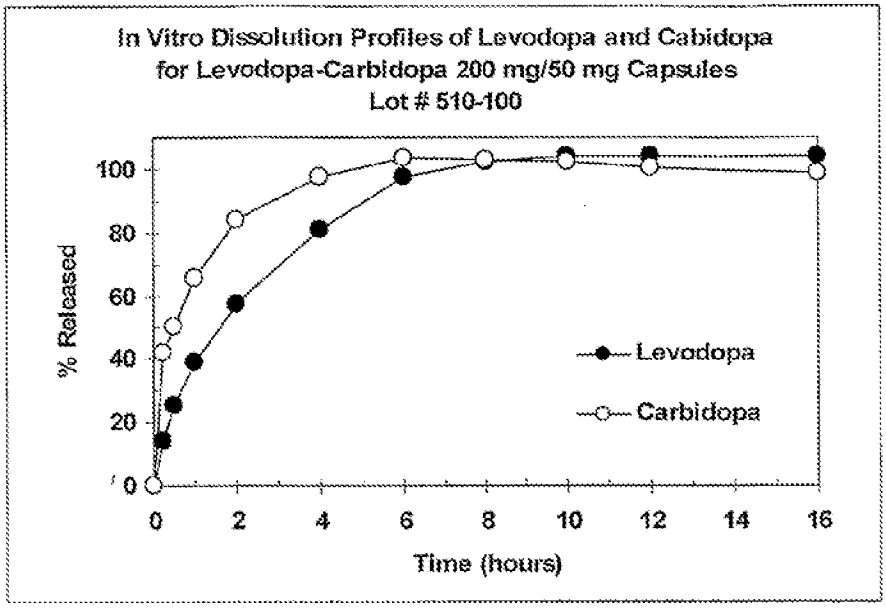

In Vitro Dissolution Profiles of Levodopa and Cabidopa
for Levodopa-Carbidopa 200 mg/50 mg Capsules
Lot # 510-100
% Released
100
80
60
40
20
0
0
2
4
6
8
10
12
14
16
Time (hours)
Levodopa
Carbidopa

FIG. 79

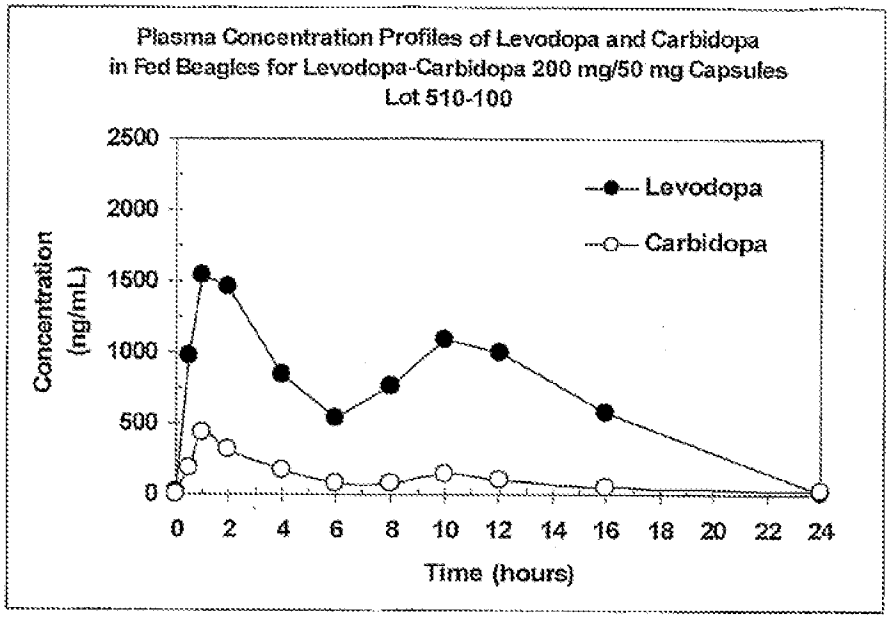

Plasma Concentration Profiles of Levodopa and Carbidopa
in Fed Beagles for Levodopa-Carbidopa 200 mg/50 mg Capsules
Lot 510-100
Concentration (ng/mL)
2500
2000
1500
1000
500
0
Levodopa
Carbidopa
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)

FIG. 80

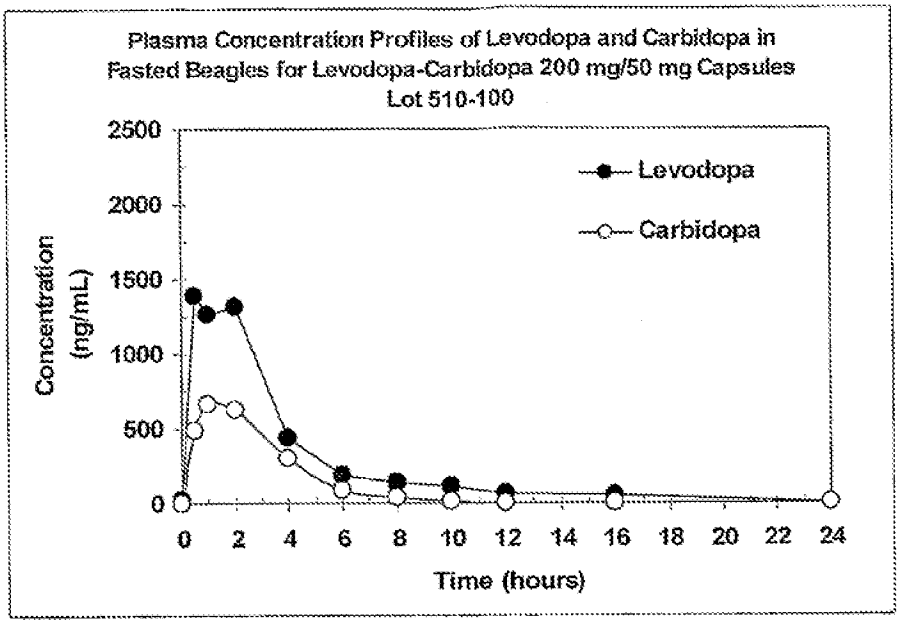

Plasma Concentration Profiles of Levodopa and Carbidopa in Fasted Beagles for Levodopa-Carbidopa 200 mg/50 mg Capsules Lot 510-100
Concentration (ng/mL)
2500
2000
1500
1000
500
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)
Levodopa
Carbidopa

FIG. 81

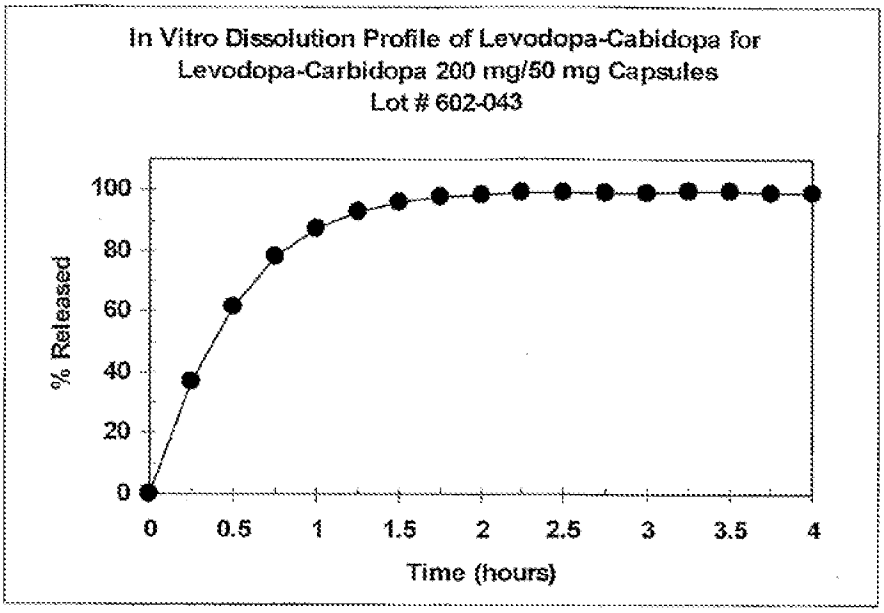

In Vitro Dissolution Profile of Levodopa-Cabidopa for
Levodopa-Carbidopa 200 mg/50 mg Capsules
Lot # 602-043
% Released
100
80
60
40
20
0
0
0.5
1
1.5
2
2.5
3
3.5
4
Time (hours)

FIG. 82

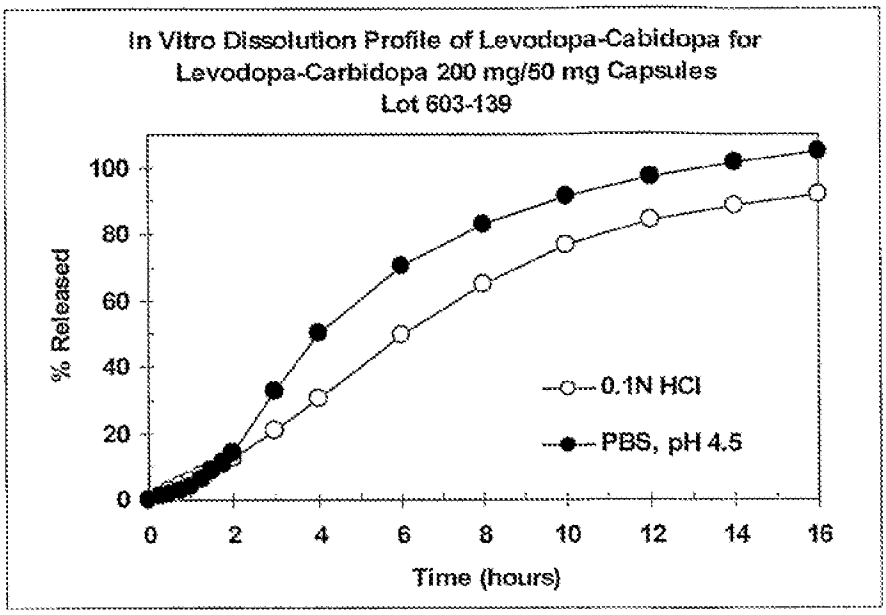

In Vitro Dissolution Profile of Levodopa-Cabidopa for
Levodopa-Carbidopa 200 mg/50 mg Capsules
Lot 603-139
% Released
100
80
60
40
20
0
0
2
4
6
8
10
12
14
16
Time (hours)
0.1N HCl
PBS, pH 4.5

FIG. 83

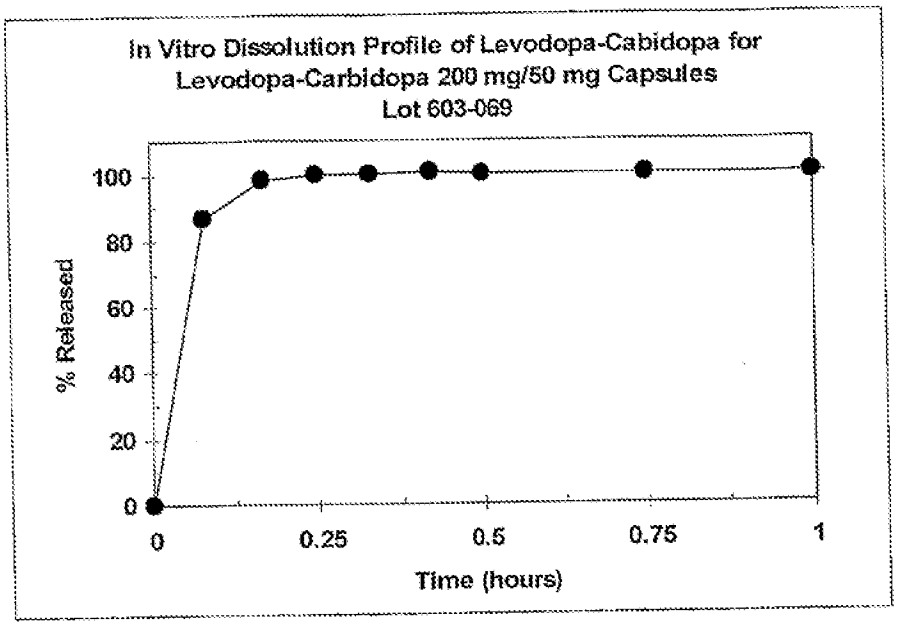

In Vitro Dissolution Profile of Levodopa-Cabidopa for
Levodopa-Carbidopa 200 mg/50 mg Capsules
Lot 603-069
% Released
100
80
60
40
20
0
0
0.25
0.5
0.75
1
Time (hours)

FIG. 84

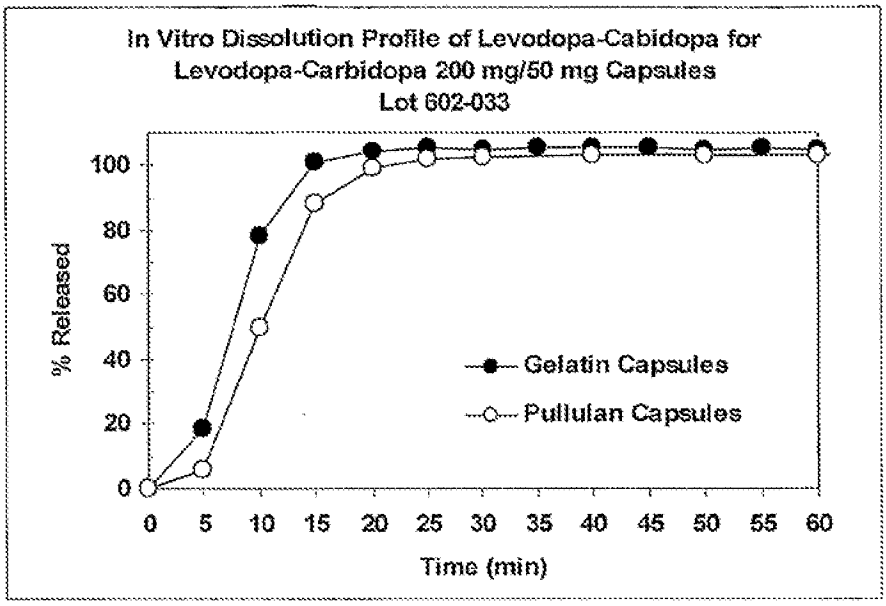

In Vitro Dissolution Profile of Levodopa-Cabidopa for
Levodopa-Carbidopa 200 mg/50 mg Capsules
Lot 602-033
% Released
100
80
60
40
20
0
0 5 10 15 20 25 30 35 40 45 50 55 60
Time (min)
Gelatin Capsules
Pullulan Capsules

FIG. 85

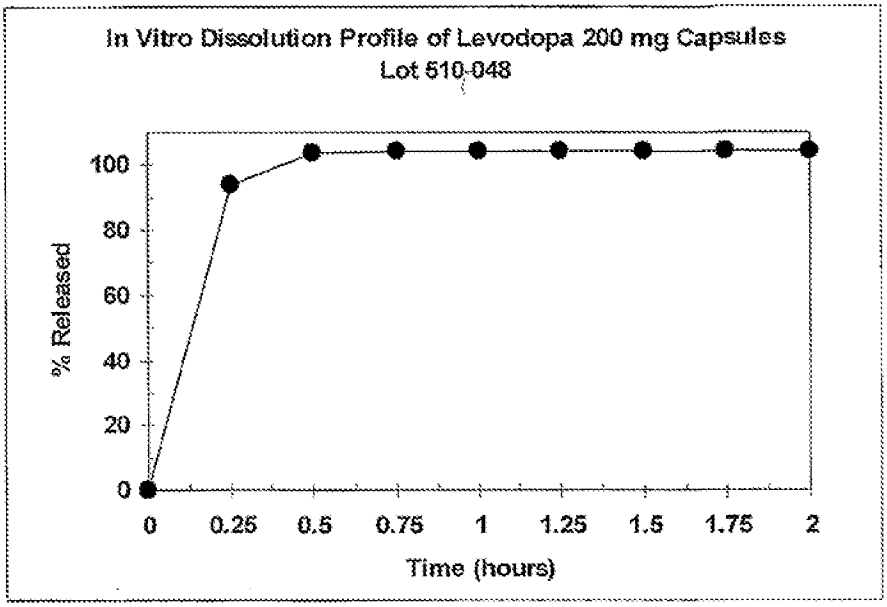

In Vitro Dissolution Profile of Levodopa 200 mg Capsules
Lot 510-048
% Released
100
80
60
40
20
0
0
0.25
0.5
0.75
1
1.25
1.5
1.75
2
Time (hours)

FIG. 86

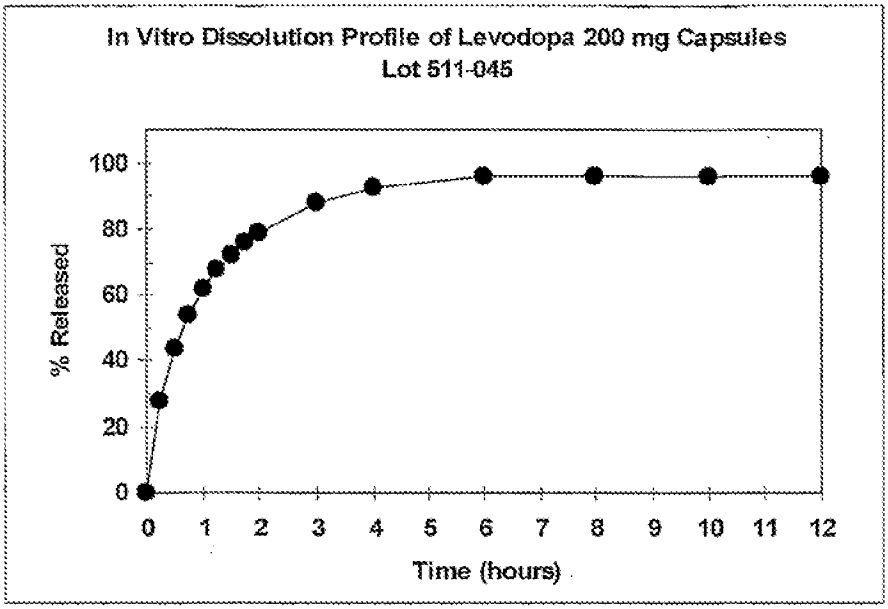

In Vitro Dissolution Profile of Levodopa 200 mg Capsules
Lot 511-045
% Released
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12
Time (hours)

FIG. 87

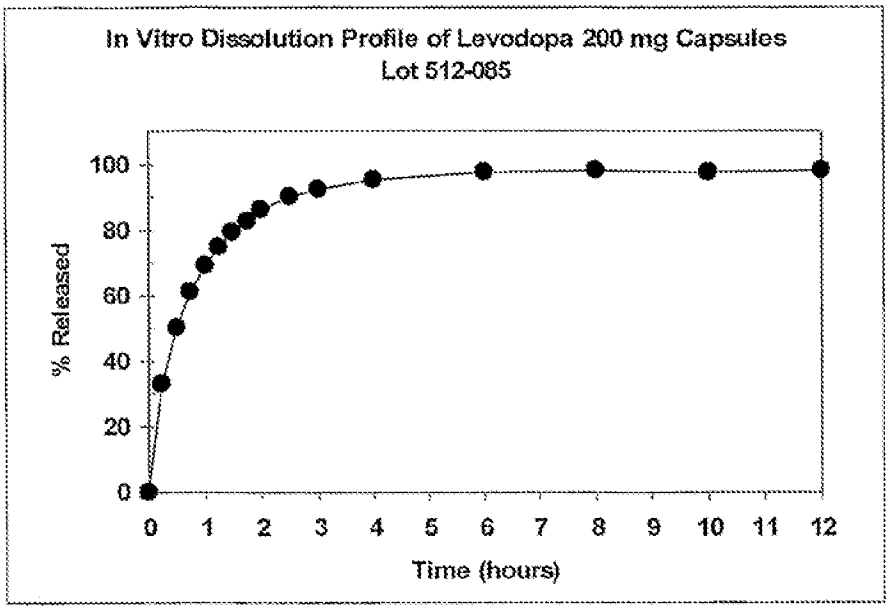

In Vitro Dissolution Profile of Levodopa 200 mg Capsules
Lot 512-085
% Released
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12
Time (hours)

FIG. 88

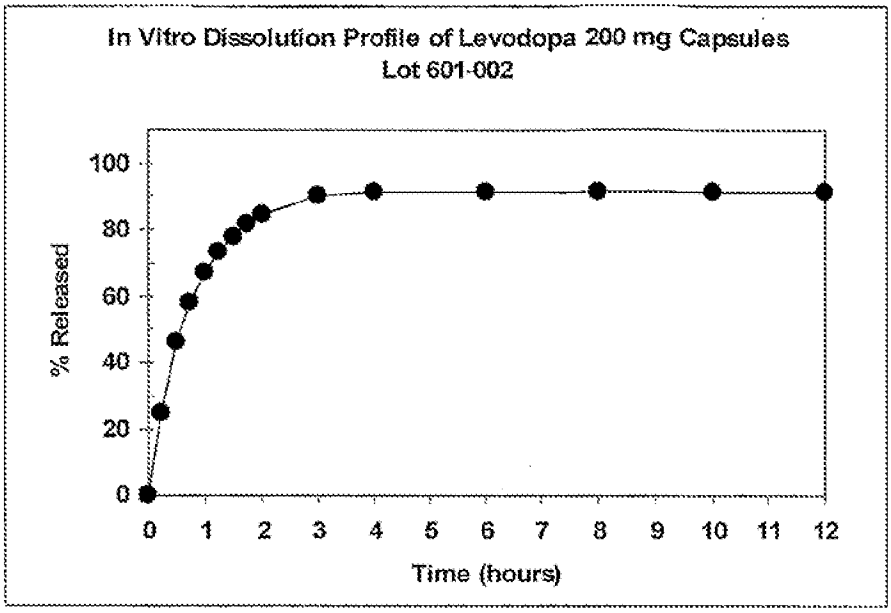

In Vitro Dissolution Profile of Levodopa 200 mg Capsules
Lot 601-002
% Released
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12
Time (hours)

FIG. 89

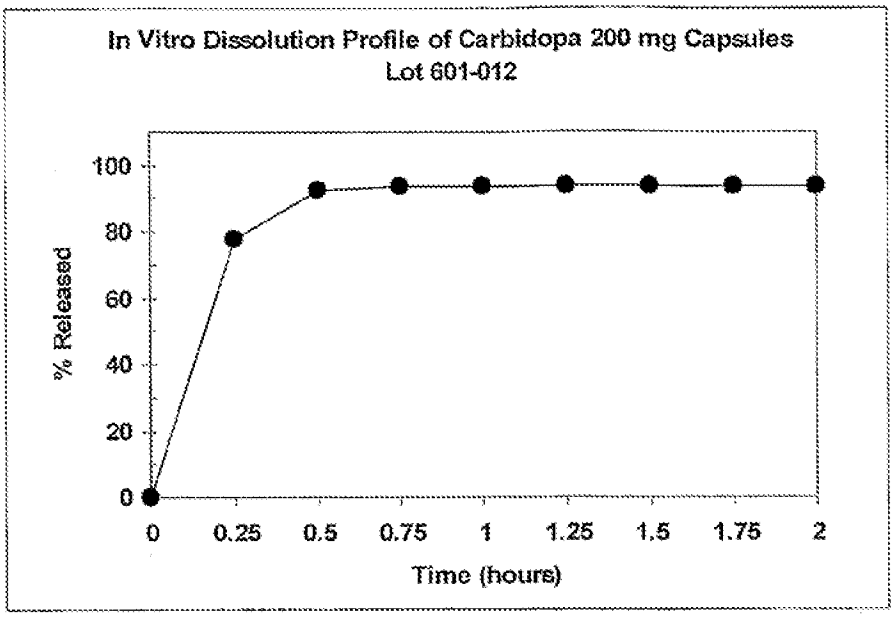

In Vitro Dissolution Profile of Carbidopa 200 mg Capsules
Lot 601-012
% Released
100
80
60
40
20
0
0
0.25
0.5
0.75
1
1.25
1.5
1.75
2
Time (hours)

FIG. 90

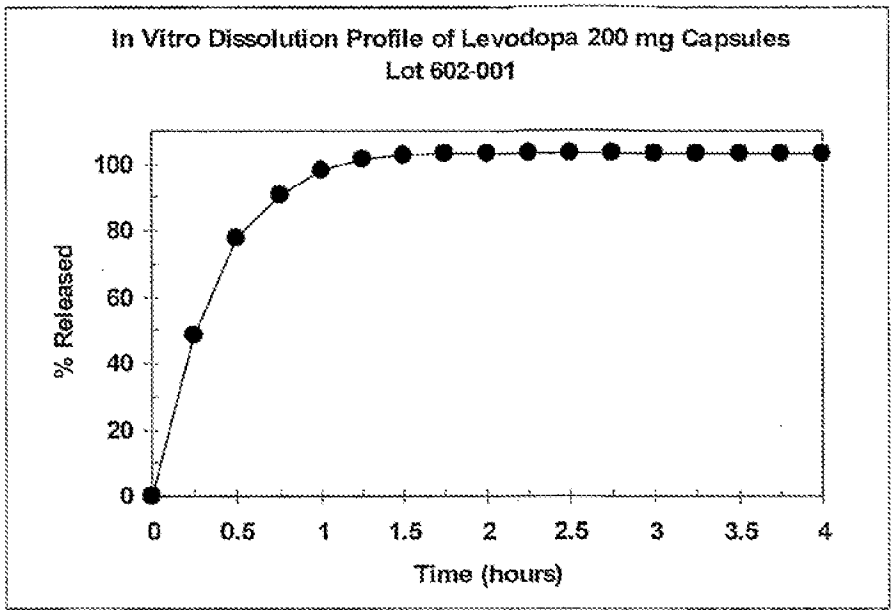

In Vitro Dissolution Profile of Levodopa 200 mg Capsules
Lot 602-001
% Released
100
80
60
40
20
0
0
0.5
1
1.5
2
2.5
3
3.5
4
Time (hours)

FIG. 91

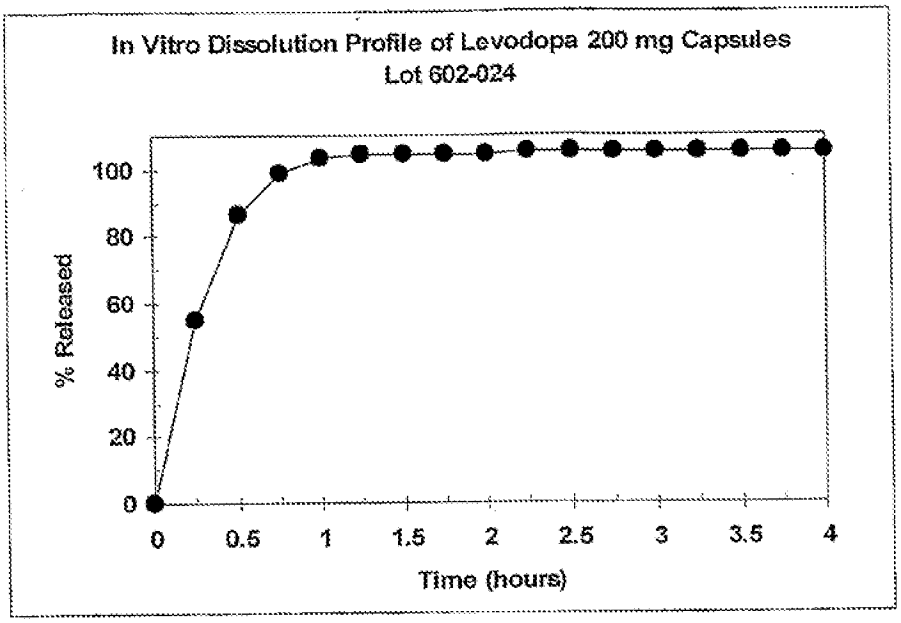

In Vitro Dissolution Profile of Levodopa 200 mg Capsules
Lot 602-024
% Released
100
80
60
40
20
0
0
0.5
1
1.5
2
2.5
3
3.5
4
Time (hours)

FIG. 92

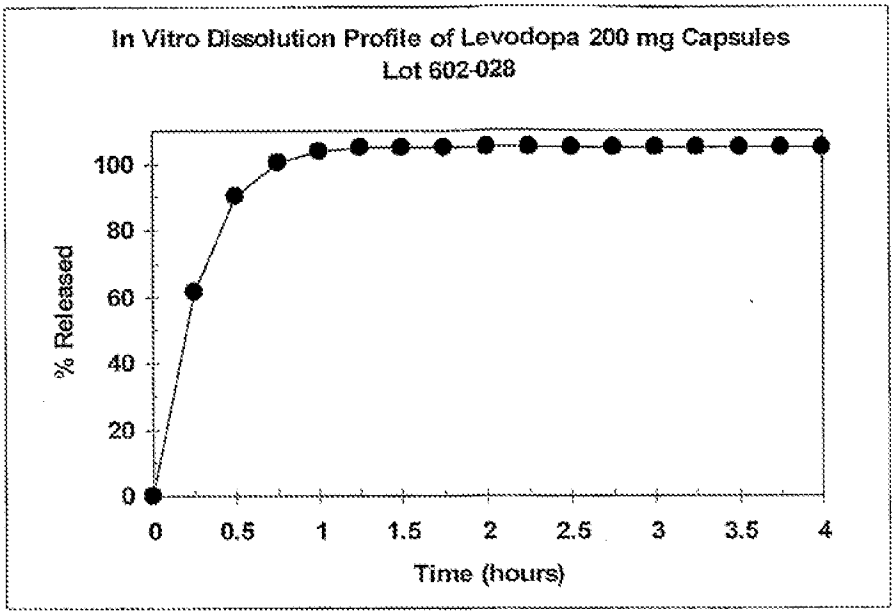

In Vitro Dissolution Profile of Levodopa 200 mg Capsules
Lot 602-028
% Released
100
80
60
40
20
0
0
0.5
1
1.5
2
2.5
3
3.5
4
Time (hours)

FIG. 93

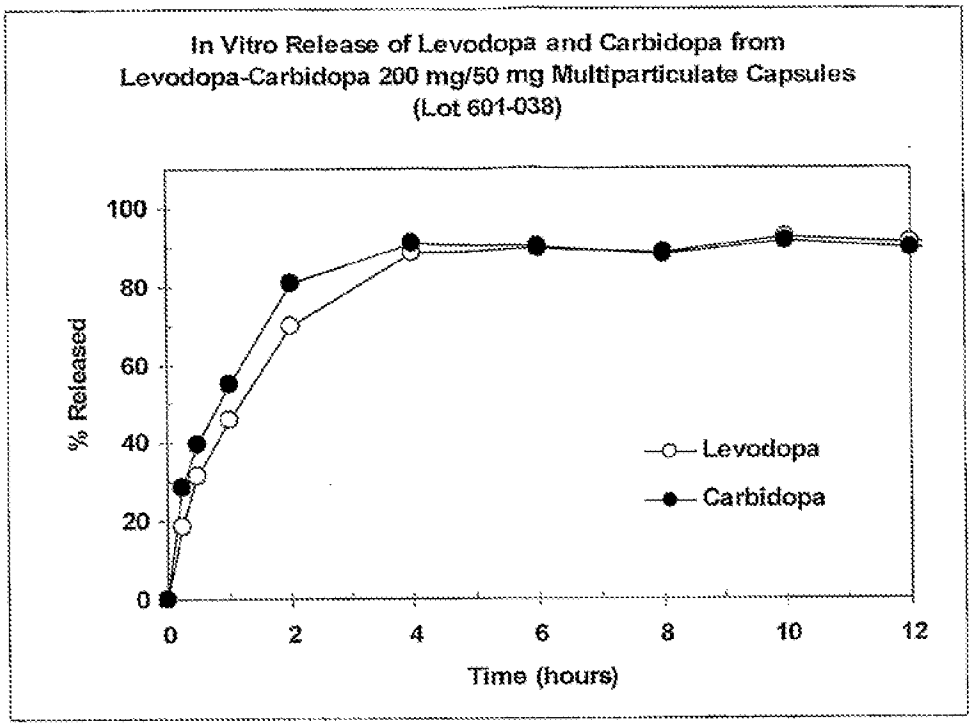

In Vitro Release of Levodopa and Carbidopa from
Levodopa-Carbidopa 200 mg/50 mg Multiparticulate Capsules
(Lot 601-038)
% Released
100
80
60
40
20
0
0
2
4
6
8
10
12
Time (hours)
Levodopa
Carbidopa

FIG. 94

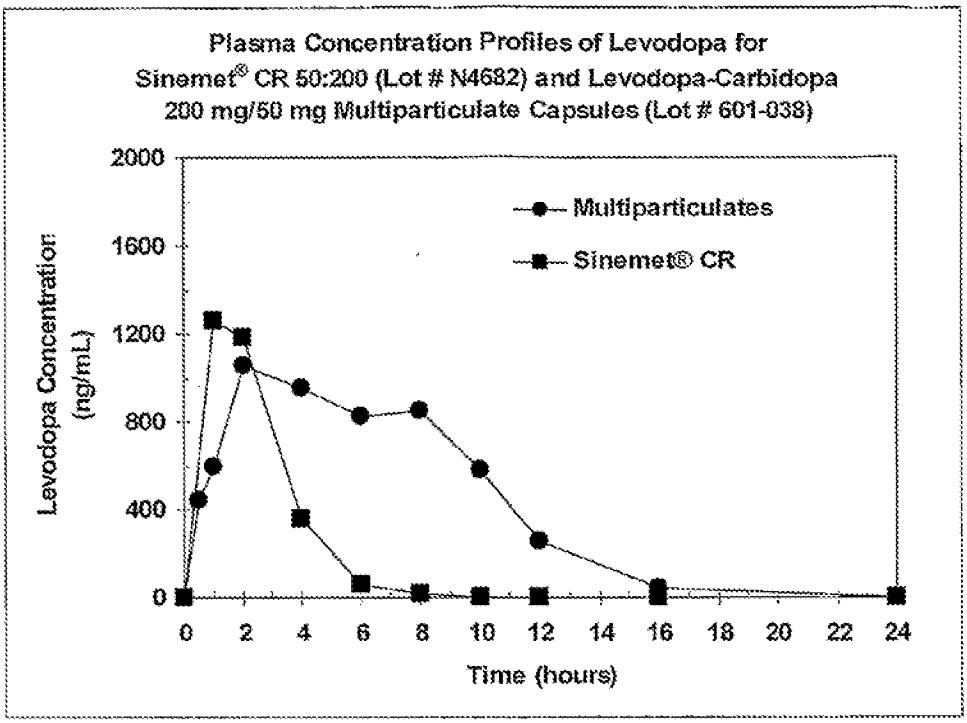

Plasma Concentration Profiles of Levodopa for
Sinemet® CR 50:200 (Lot # N4682) and Levodopa-Carbidopa
200 mg/50 mg Multiparticulate Capsules (Lot # 601-038)
Levodopa Concentration (ng/mL)
2000
1600
1200
800
400
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)
Multiparticulates
Sinemet® CR

FIG. 95

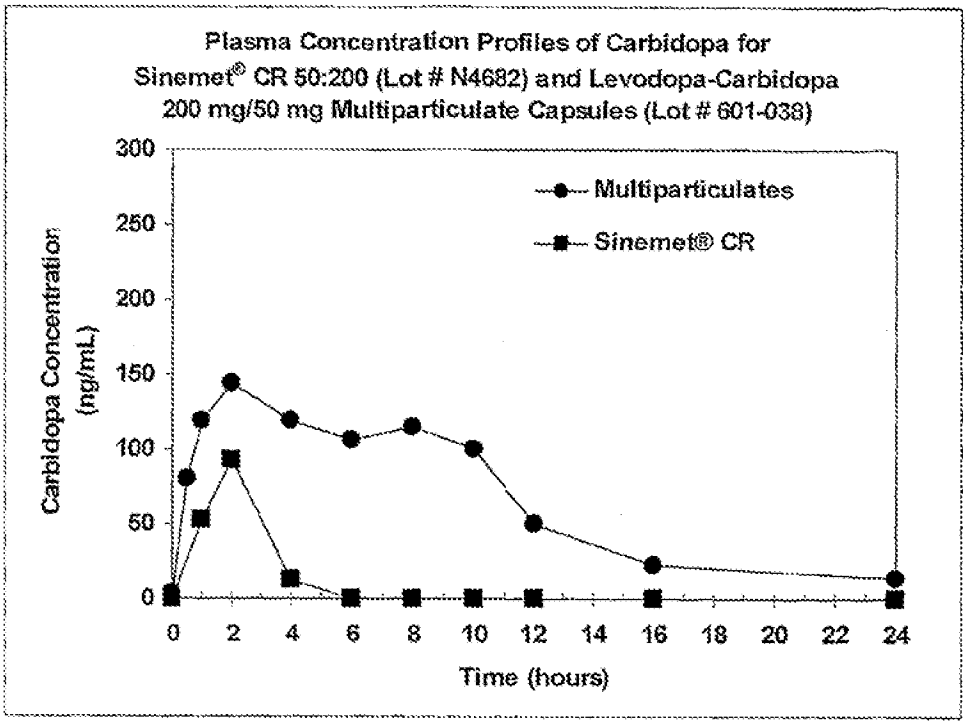

Plasma Concentration Profiles of Carbidopa for
Sinemet® CR 50:200 (Lot # N4682) and Levodopa-Carbidopa
200 mg/50 mg Multiparticulate Capsules (Lot # 601-038)
Carbidopa Concentration (ng/mL)
300
250
200
150
100
50
0
0 2 4 6 8 10 12 14 16 18 20 22 24
Time (hours)
Multiparticulates
Sinemet® CR

FIG. 96

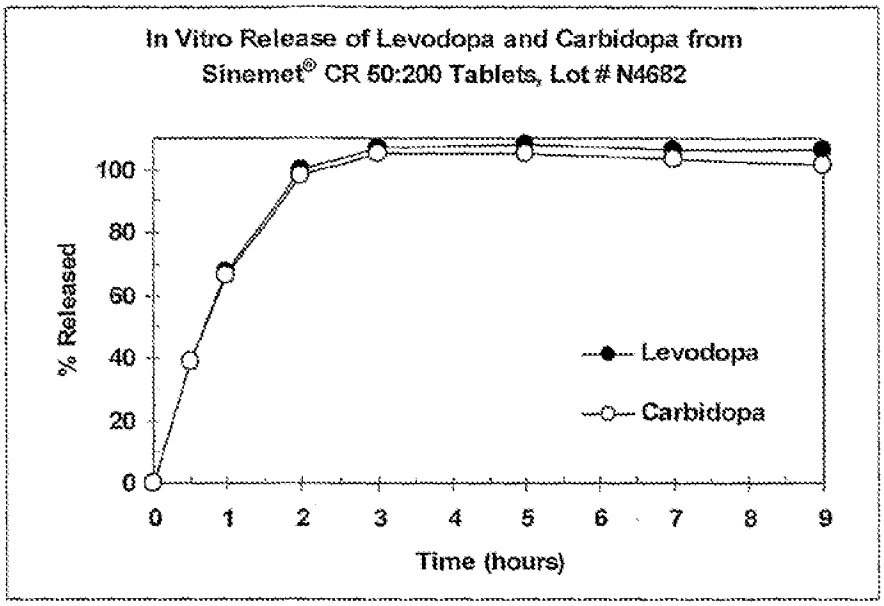
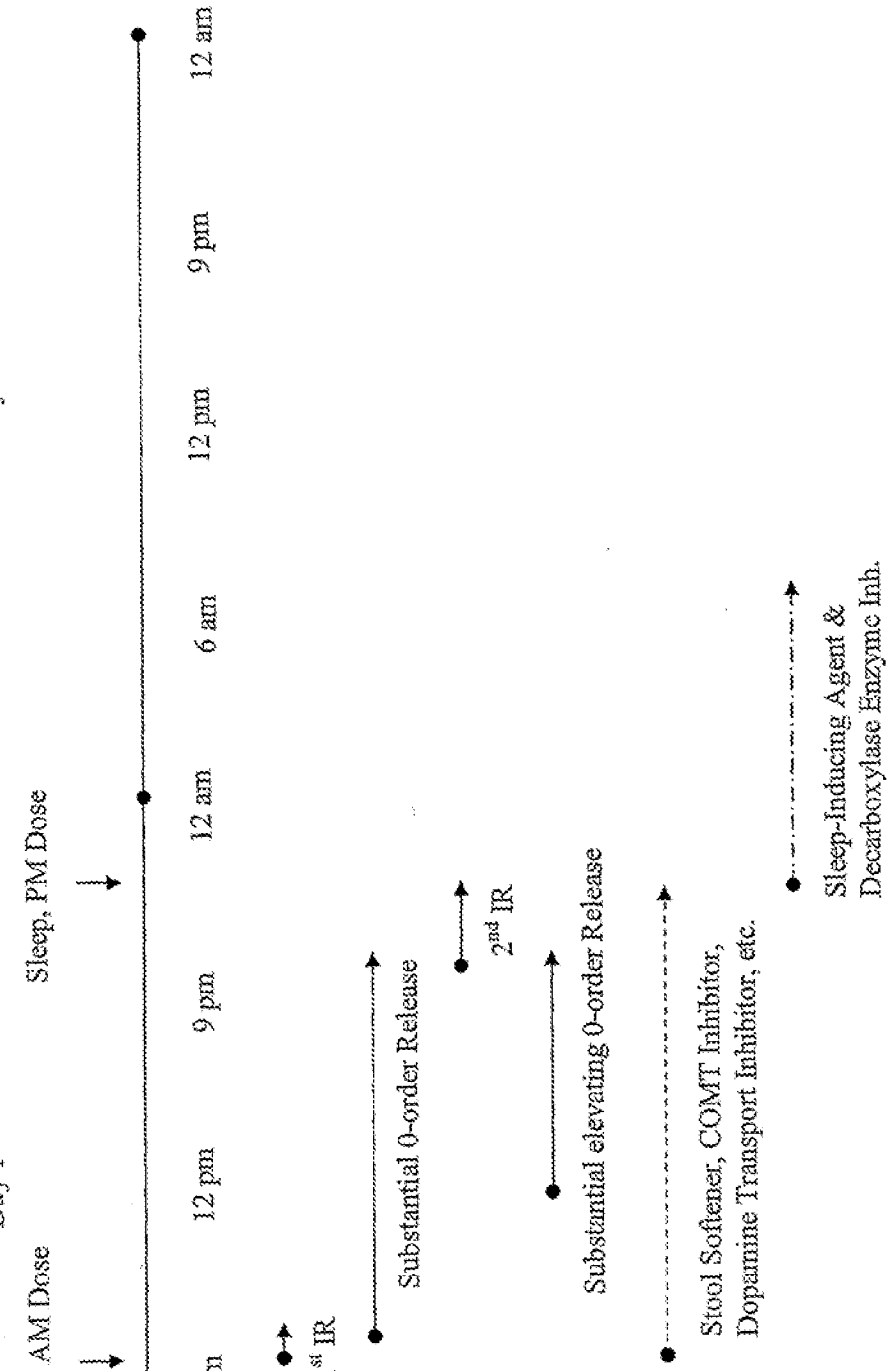

In Vitro Release of Levodopa and Carbidopa from
Sinemet® CR 50:200 Tablets, Lot # N4682
% Released
100
80
60
40
20
0
0
1
2
3
4
5
6
7
8
9
Time (hours)
Levodopa
Carbidopa

FIG. 97


Day 1
Day 2
Wake Up, AM Dose
Sleep, PM Dose
12 am
6 am
12 pm
9 pm
12 am
6 am
12 pm
9 pm
12 am
1st IR
Substantial 0-order Release
2nd IR
Substantial elevating 0-order Release
Stool Softener, COMT Inhibitor,
Dopamine Transport Inhibitor, etc.
Sleep-Inducing Agent &
Decarboxylase Enzyme Inh.